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PLACENTA ACCRETA: CLINICAL MANIFESTATIONS AND CONSERVATIVE MANAGEMENT*

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HEMORRHAGE associated with pregnancy is still responsible for the majority of maternal deaths. Even though in recent years this group of deaths has been materially diminished by improved obstetrical care, much could be done to enlighten the practitioner about the less common causes of intra-partum and post-partum hemorrhage.

Placenta accreta is one of the less common conditions associated with hemorrhage in pregnancy. In fact, some obstetricians of long experience have never seen a case of it. However, when one learns of a reported mortality rate of 37 to 67 per cent associated with it, one must accept placenta accreta as a dangerous entity.

Any disease commanding such a high mortality rate should, ordinarily, stimulate considerably more interest in research and accumulation of data than is found in current literature or textbooks. No attempt is made to point out symptoms that may lead one to suspect and be prepared for the development of placenta accreta during pregnancy. The management is even more confused, ranging from strict conservatism, as exemplified by watchful waiting, to immediate hysterectomy on the presumptive evidence of an accreta.

In the past ten years very few publications on placenta accreta have appeared. We believe, therefore, that a presentation of the subject at this time, with a report of our clinical observations on symptoms, clinical manifestations and management, will be both timely and contributory to the knowledge of this important and serious cause of hemorrhage.

DEFINITION

"Placenta accreta" is a generic term used to designate those conditions in which no line of cleavage between placenta and uterine wall can be found.

Where a very thin layer of decidua or none exists, the condition is called "placenta accreta vera." "Placenta increta" results when not only the decidua is scant or absent but also the chorionic villi penetrate deeply into the myometrium. The term "placenta percreta" is reserved for those cases in which the chorionic villi have perforated the uterine wall.

These conditions may be focal, partial or complete, depending on how much of the placenta is involved in the pathologic process.

HISTORY

The first reported case, according to Plater,[1] occurred in the year 88 A.D. The placenta was retained and the patient died. At necropsy the placenta was found to be firmly adherent to the internal os.

Langhans' discovery that placental separation takes place in the spongy layer of the decidua was reported in 1875. Hart[2] arrived independently at this conclusion in 1889 and in addition gave the first microscopical account of placenta accreta,[3] stating that the spongy layer of the decidua was absent.

The first patient to recover was reported by Alexandroff[4] in 1900. A spontaneous rupture of the uterus occurred secondary to a placenta percreta. A hysterectomy was performed and the underlying condition was discovered on examination of the specimen.

Because much of the literature on placenta accreta has originated in this vicinity, and since this area has reported a far higher incidence of placenta accreta than has been found elsewhere, the condition has sometimes been referred to as "the Boston disease."

PATHOLOGY

In the case of a hysterectomy specimen, close examination of the organ reveals an intimate fusion of the placenta and uterine wall. They are so adherent that no real line of demarcation can be found. When the specimen is a manually removed placenta, one may find bits of muscle adherent to the maternal surface of the organ.

Microscopically, the most prominent feature of placenta accreta is the partial or complete absence of the decidua basalis. The decidual coat being

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defective, the chorionic villi must attach themselves directly to the myometrium.

It is the absence of the spongy layer of the decidua that gives rise to the clinical phenomena associated with the condition. Since the normal separation of the placenta takes place by a cleavage through this spongy layer, it is clear that if this layer is absent or defective separation becomes difficult, if not impossible.

Placenta accreta is often associated with other abnormalities of the placenta, including placenta membranacea, placenta succenturiata and placenta previa.

Incidence

Statistics vary greatly concerning the relative frequency of placenta accreta. Nathanson[5] found an incidence of one in 20,000 deliveries. The Boston Lying-in Hospital reports one in 1956 confinements. Irving and Hertig[4] believe that many cases do not appear in the literature, this being particularly true of partial and focal placenta accreta. Further weight is given to this theory by their findings of partial twice as often as complete accreta, whereas the literature reports a relative preponderance of the complete form.

The disease is primarily one of multiparity. Of the 18 cases reported by Irving and Hertig, all but one were in multiparas.

Etiology

There is universal agreement about the importance that endometrial trauma plays in the subsequent development of placenta accreta. However, any condition that would produce an atrophy or absence of the normal decidua might be considered a causative factor.

Table 1. *Etiology of Placenta Accreta.*

Uterine Factors	Placental Factors
Congenital anomalies	Abnormal location
Absence of decidua	Cornual implantation
Diverticula, uterine	Previa (1)*
Endocrine: defective C. luteum	Development defect
Infection	Membranacea (1)
Endometritis	
Pyometrium	
Trauma	
Cesarian section (1)	
Caustic agents	
Curettage (5)	
Hysterotomy	
Irradiation, intrauterine	
Manual removal of placenta	
Vaporization treatment	
Tumor	
Fibromyoma, submucous	

*The parenthetical numbers refer to the number of times that the authors believe these factors to have been operative in the series of cases here reported.

The factors to be considered are shown in Table 1.

Symptoms

There is no mention in the literature of any complaints of the patient that have occurred frequently enough to be definitely associated with placenta accreta. As recently as 1947 the statement was made[7] that the symptoms of placenta accreta are silent.

It is significant, however, that Potter's patient[8] experienced four acute attacks of lower-abdominal pain during her first four months of pregnancy, requiring morphia. Davidson's patient[9] was seized with sudden excruciating cramp-like pains, as though expulsion were imminent, although examination revealed dilatation of only 2 fingerbreadths.

Hegar[10] theorized that fibrosis secondary to hemorrhage with early threatened miscarriages played a role in the production of placenta accreta. This indicates that at least some of these pregnancies had survived cramping abdominal pains early in the gestation that had been interpreted as indicating threatened miscarriages.

One of our patients suffered severe lower-abdominal pain during the last two months of her pregnancy. During this time she was unable to perform any of her usual household duties because of the pain and was confined to bed. She was hospitalized for two days prior to her delivery, and during this period she was several times reported to be in hard labor with expulsive efforts, but examination disclosed the presenting part to be unengaged.

In another instance, a victim of severe migraine attacks reports that the lower-abdominal pain from which she suffered during the three months preceding her miscarriage at five and a half months was "like labor pains, but far worse."

A third patient was subject to intermittent severe cramping lower-abdominal pain during the first three months of her pregnancy. Furthermore, on the two days preceding her delivery she suffered from intermittent abdominal pains that were "ten times harder than labor pains," — this from a woman who had had four previous labors and deliveries without benefit of sedation or anesthesia.

The authors believe that a patient with retained products of conception who has a history of unusually severe labor-like pains during the gestation should be treated with especial care as a possible candidate for placenta accreta. They further believe that patients with a history of intrauterine manipulation should be questioned about abdominal pain during the prenatal period.

Differential Diagnosis

Phaneuf,[11] as well as Rutherford and Hertig,[12] has done much to clarify the findings in cases superficially suggestive of placenta accreta. The conditions that must be distinguished from placenta accreta are found in Table 2.

Diagnosis

Placenta accreta should be entertained as a possible diagnosis when there is retention of the placenta accompanied by a lack of the signs of separa-

tion after a reasonable period of time. It should be considered in cases of late post-partum bleeding. It must be kept in mind in all cases of incomplete miscarriage and retained secundines.

The positive diagnosis of the condition can be made only on the basis of failure to find a line of cleavage between the placenta and uterine wall on intrauterine manual examination. This diagnostic procedure should be carried out with the greatest of caution and only after adequate preparations have been made for blood transfusion and laparotomy.

TABLE 2. *Differential Diagnosis.*

Postabortal
Incomplete miscarriage
Intra-partum
Retained separated placenta (incarcerated)
Retained adherent placenta
Post-partum
Retained secundines
Subinvolution of placental site

MANAGEMENT

Perusal of the literature discloses that among the writers conversant with the subject of placenta accreta many favor hysterectomy as the treatment of choice, once the diagnosis has been established.[12] This is irrespective of the occasional report[14, 15] of survival after conservative management.

The majority of writers do not believe that hysterectomy is warranted in all cases of retained placenta unless it is first established that manual removal is impossible. This is in opposition to those[16, 17] who advocate hysterectomy without intrauterine examination as the treatment of placenta accreta because of the low mortality rate associated with the single procedure. Most writers believe that if adequate preparations for blood transfusion and laparotomy are made prior to the vaginal examination and if, as Conti[18] stresses, the attempt at manual extraction is promptly abandoned once no line of cleavage is found the mortality of the combined procedure may well approach that of simple hysterectomy.

Reports[19-26] have recently appeared of cases in which manual examination revealed no line of cleavage between placenta and uterine wall. Manipulation was stopped and the patient treated expectantly. The reported results were excellent.

The authors disagree with the general opinion that hysterectomy is the treatment of choice in placenta accreta and that attempted manual removal of the placenta is to be condemned. They believe that the majority of the cases can be handled conservatively without undue maternal risk. The cases presented herewith substantiate this view.

CONSERVATIVE THERAPY

The rationale of the conservative therapy is expressed as follows:

Placenta accreta is not always recurrent. Two cases in our series prove this point, and there are others in the literature.[14, 25] Therefore, one should not adopt the attitude that any future pregnancy must necessarily be a threat to the patient's life.

Former radical management of potentially infected maternity cases is obviated by present-day antibiotics. We do not believe that this premise needs specific proof. The persistent decline in the number of maternal deaths due to infection speaks for itself.

The possibility of neoplasm in the residual placental tissue is too remote to influence the management of any acute obstetrical problem. In these cases the aim is to manage the emergency in the manner best calculated to bring the patient through alive. Minor possibilities should not be allowed to sway judgment in such dire emergencies.

TABLE 3. *Management.*

TREATMENT	NO. OF CASES	MORBIDITY		DEATHS	
		NO.	%	NO.	%
Manual examination; hysterectomy	1	0	0	0	0
Manual extraction; dilatation and curettage	1	1	100	0	0
Manual extraction	7	2	29	0	0
Dilatation and curettage	1	0	0	0	0
Dilatation and curettage; hysterectomy	2	0	0	0	0
Hysterectomy	1	0	0	1	100
	13	3	23	1	7.7

The bleeding associated with placenta accreta does not ordinarily originate spontaneously at the site of the accreta.

In complete placenta accreta there is ordinarily no excessive bleeding unless repeated Crede maneuvers or attempted manual extraction has been employed. This fact is repeatedly confirmed in the literature.[10] Where there is little bleeding and vaginal examination confirms the impression of complete accreta we believe that the cord should be tied short and cut and the patient treated expectantly. The logic of leaving the placenta in situ, based as it is on the accepted management of the placenta in abdominal pregnancy (really another form of placenta accreta), is indisputable. When there is bleeding, one should prepare for blood replacement and laparotomy. As much as possible of the bulk of the placenta should be removed in order to facilitate contraction of the uterus. Oxytocics should be administered and blood replacement carried out. If bleeding persists or recurs, further attempts at manual extraction, curettage or hysterectomy may be indicated.

Partial placenta accreta presents a different problem. Here the hemorrhage is usually prompt and profuse. In this instance the bleeding comes not from the area of the accreta but from adjacent areas where placental separation has taken place, — where sinuses remain open because effective uterine contractions are prevented by the retained placenta. Here removal of the separated portion of the placenta should be instituted with extraction of as much as possible of the tissue overlying the accreted portion. Again oxytocics should be administered, blood replacement carried out and the patient watched. Curettage or hysterectomy may be indicated by bleeding later in the post-partum period.

TABLE 4. *Summary of Management.*

TREATMENT	NO. OF CASES	MORBIDITY		DEATHS	
		NO.	%	NO.	%
Hysterectomy	4	0	0	1	25
Conservative	9	3	33	0	0
	13	3	23	1	7.7

Conservatism, therefore, can be abandoned in favor of hysterectomy if hemorrhage is persistent. One need not adopt conservatism to the exclusion of hysterectomy. One can and should remove the uterus if bleeding persists.

The problem of management is then dependent on the amount of bleeding and on its response to the removal of as much as possible of the placenta.

In some cases profuse hemorrhage attends attempted removal of the placenta. In such situations blood replacement and prompt hysterectomy should be carried out.

More commonly extensive, grossly unsuccessful attempts at removal of the placenta are productive of amazingly little bleeding. In these cases nothing is lost by temporizing if the attendant is adequately prepared for blood replacement and radical intervention in the event of sudden bleeding.

When there is little or no bleeding several days after the emergency no further manipulation should be carried out, even when abundant placental tissue is readily palpable through an open cervix.

We believe that the diminished percentage of confirmatory microscopical reports that will necessarily result from the adoption of conservative management will be more than balanced by an increased maternal salvage and the preservation of normal physiologic function and childbearing potentialities. Table 3 presents the various methods employed in managing this series of cases with the accompanying morbidity and mortality.

Because of an unfortunate outcome in one case, the mortality percentage for the cases in which hysterectomy was carried out is falsely high. Nine cases were managed conservatively with no maternal mortality. We believe that this represents what can be accomplished under present-day conditions and certainly establishes the fact that the tremendous mortality formerly associated with conservative treatment is no longer applicable.

MORBIDITY

The authors do not believe that statistics on morbidity and mortality that include earlier cases should be used as the basis for any conclusions concerning present-day management.

TABLE 5. *Summary of Cases.*

CASE NO.	AGE	PARITY	GRAVIDITY	POSSIBLE ETIOLOGY	NO. OF WEEKS OF PREGNANCY	SYMPTOMS PRESENT	DELIVERY	POSTPARTUM HEMORRHAGE
1	27	I	III	D & C	36	Yes	Normal	Yes
2	25	III	IV	D & C	38	No	Normal	Yes
3	29	0	VI	5 D & C	35	No	Low forceps	No
4	32	II	IV	D & C	38	No	Normal	Yes
5	31	IV	V	—	38	No	Normal	Yes
6	32	I	II	Scar	37	No	Cesarian section	No
7	20	II	III	—	38	No	Normal	Yes
8	27	0	I	—	22	No	Normal	Yes
9	30	III	IV	2 D & C	31	No	Internal podalic version	Yes
10	39	II	III	—	20	Yes	Normal	No
11	38	V	VII	—	38	Yes	Normal	No

Although earlier writings reported many complications such as peritonitis, gangrene, pelvic cellulitis and thrombophlebitis, the more recent reports indicate that infection is playing a progressively less important role in placenta accreta.

Three of the cases here presented fall into the classification of morbidity, — an incidence of 23 per cent. The fever of one of these patients was due to a severe reaction to blood transfusion, with accompanying oliguria and hematuria. Another

patient had her highest temperature twelve hours before delivery and a tender, presumably necrosing fibroid. Thus, we have only one patient whose morbidity can be reasonably traced to her accreta, — a corrected incidence of 7.7 per cent.

A review of the patients' clinical charts shows an amazing lack of febrile reaction, for the most part, some of the most seriously ill patients showing no variation from normal temperature during the post-partum period despite their being in extremis during the emergency.

The patients' recovery after adequate treatment was unbelievably rapid, simulating the recovery from surgical shock in patients operated on for ruptured tubal pregnancy once the hemorrhage has been controlled.

Mortality

The cases reported prior to 1937 showed a combined mortality of 37 per cent. This included all the various methods of management.

In the pre-1937 era, cases in which the operator attempted removal of the placenta either by manual extraction or curettage were attended by a 65 per cent mortality rate. The present paper describes a total of 8 manual extractions and 4 curettages without a death.

The only fatality in our series occurred in a patient treated by hysterectomy in whom the placenta was found to be attached to the uterine scar resulting from a previous low classical cesarian section. This patient died suddenly one hour after being returned to her room in good condition, — probably of pulmonary embolism. This represents an over-all mortality rate of 7.7 per cent for the series and of 25 per cent for those cases treated by hysterectomy.

Summary of Cases

Age. These patients tended to be older than the general run of obstetrical patients, having an average age of 30 years.

Parity. This series bears out the fact that the disease is primarily one of multiparity only two of the patients being primiparous and one of these a gravida vi.

Etiology. The well known factor of previous endometrial trauma is well borne out by the positive histories in 6 of our cases. The fact that careful questioning failed to elicit any such story in 5 cases emphasizes the fact that many other factors are undoubtedly operating in these cases.

Symptoms. This matter has been previously discussed. There was a positive history of severe abdominal pain during pregnancy in three of the cases.

Duration of pregnancy. Of the 13 pregnancies, 7 (54 per cent) were at term. Ten were over eight months (77p er cent). One patient was thirty-one weeks, one was twenty-two weeks and one was twenty weeks pregnant.

Delivery. Eleven of the 14 deliveries were normal (78 per cent). There was one cesarian section, one low-forceps delivery and one internal podalic version.

Post-partum hemorrhage. There was spontaneous post-partum hemorrhage in 7 of the 13 cases (54 per cent). In some cases this was not profuse but persistent. In two cases it was late in the puerperium.

Table 5 (*Concluded*).

Case No.	Accreta	Diagnosis Confirmed Microscopically	Treatment	Maternal Results	Fetal Results	Remarks
1	Partial	Yes	D & C Hysterectomy	Living	Living	Membranacea
2	Complete	Yes	Manual extraction D & C	Living	Living	Subsequent normal pregnancy
3	Complete	Yes	Manual examination Hysterectomy	Living	Living	Increta
4	Complete	No	Three manual extractions	Living	Living	Previous accreta
5	Complete	No	Manual extraction	Living	Living	Inversion (vaginal)
6	Partial	Yes	Hysterectomy	Died	Living	? Embolism
7	Partial	No	D & C	Morbidity	Living	Inversion (abdominal)
8	Complete	Yes	Manual extraction	Living	Died	Subsequent miscarriage at 5 mo. (no accreta)
9	Partial	No	Manual extraction	Morbidity	Stillborn	Previa
10	Partial	No	Manual extraction	Morbidity	Stillborn	Twins Fibroid uterus
11	Partial	Yes	D & C Hysterectomy	Living	Living	Normal parturition Hemorrhage 6 wk. post partum

Extent of the disease. Of the 13 cases, there were 7 instances of complete accreta and 6 of partial. There was 1 partial increta.

Microscopical confirmation. This was obtained in 6 of the cases, in 4 of which hysterectomy had been performed.

Management. In the management of the series there were 4 hysterectomies and 9 conservatively managed cases. In the latter group there were 8 manual extractions, 2 replacements of inverted uteri (one vaginal, one abdominal) and 2 curettages later in the puerperium. Of the cases treated by

hysterectomy, 1 followed a repeat cesarian, 1 followed attempted manual extraction with profuse bleeding and 2 followed failure of curettage to control the hemorrhage.

Maternal results. Of the 11 mothers 10 lived; 3 of these had complications. The subsequent histories of the conservatively managed cases disclose that 1 patient had a subsequent uneventful pregnancy. One had 2 subsequent term deliveries with recurrent placenta accreta, followed by 2 incomplete miscarriages. A third had a five-months miscarriage with a retained adherent placenta.

Fetal results. Of the 14 babies, 4 were stillborn (3 macerated, 1 hydrocephalic) and 10 (71 per cent) were living. One of the living babies later died of prematurity.

Morbidity. Three patients had complications, an incidence of 23 per cent for the series and 33 per cent for the conservatively managed cases. The corrected morbidity was 7.7 per cent for the series and 11 per cent for the conservatively managed cases.

Mortality. One patient died. This was an incidence of 100 per cent for the case treated by hysterectomy alone, 25 per cent for the cases treated by hysterectomy at cesarian section and 7.7 per cent for the series.

Classification of patients. Five of the cases were private patients of the authors. Five patients were seen in consultation. One was a ward patient.

Discussion

There may be a difference of opinion concerning whether the diagnoses not substantiated by microscopical evidence should be included in any series of cases of placenta accreta. We believe that this disease is somewhat unique in that the attending physician employing conservative treatment — even when a manual extraction or curettage is employed — attempts to leave the seat of the condition undisturbed. He tries not to dislodge myometrium; he usually leaves large portions of placenta intact within the uterus, particularly the actual area of fusion of placenta and myometrium.

Therefore, if a negative report is obtained from the pathologist, or if by mischance a pathological investigation was not adequately carried out, one cannot refute the clinical evidence presented by the trained obstetrician. It is the obstetrician's hand that has carried out the intrauterine examination, and he knows by palpation whether all or only a part of the placenta was removed and whether the remainder is removable.

The argument that an adherent placenta might be mistaken for an accreta is not valid. In an adherent placenta there is a failure in the mechanism of separation. No great difficulty should be found in the manual separation of the placenta, however, as there is a decidual layer through which separation could and would have taken place if there had not been a physiologic failure. When separation of the placenta from the uterine wall cannot be accomplished on intrauterine examination, the placenta is not merely adherent but an accreta, and this clinical diagnosis should not be disregarded.

The symptom of unusually severe labor-like pain during the gestation is, to the authors, very significant. We do not believe that it is necessarily present in every case, nor do we contend that it is pathognomonic of placenta accreta. We wish to emphasize this finding as an important symptom to be kept in mind by the obstetrician in every case of retained products of conception.

We present no explanation of the mechanism of the pain; this is perhaps better done by the physiologist. We do not believe that it results entirely from the irritation of the myometrium. In one case, which proved to be both accreta and increta, there was only enough pain to be consistent with a threat of losing the pregnancy during the five months preceding confinement. Certainly the infiltrating increta portion of the placenta must have grossly irritated the myometrium.

Criticism is invited. We hope we may have stimulated others to investigate their cases of placenta accreta more closely, in order to substantiate or to disprove our contention concerning the value of severe abdominal pain during pregnancy as a symptom of the condition.

As to conservative management, we believe that the statistics speak for themselves. We believe that many other conservatively managed cases remain unpublished because of a lack of confirmatory microscopical evidence. We hope that other series of conservatively managed cases will be published in the future.

Conclusions

The literature in placenta accreta is briefly reviewed.

A summary of 11 varied cases of placenta accreta is presented.

The suggestion is made that a patient with retained products of conception who has a history of unusually severe labor-like pains during the gestation be treated as an especially likely candidate for placenta accreta.

A rational approach is made to the problem of management of placenta accreta, with a plea for conservatism.

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References

1. Plater, F. *Observationum in hominis . . . .* Book 1. Basileae, 1641. Pp. 231 and 232.
2. Hart, D. B. Mechanism of separation of placenta and membranes during labor. *Lab. Rep. R. C. P. Edinburgh* 1:54-61, 1889.
3. *Idem.* Contribution to pathology, symptoms, and treatment of adherent placenta. *Edinburgh M. J.* 34:816-819, 1889.
4. Alexandroff, T. Cited by Irving and Hertig.[5]
5. Nathanson, J. N. Anatomy, genesis, and clinical considerations of placenta accreta. *Am. J. Obst. & Gynec.* 16:44-50, 1928.
6. Irving, F. C., and Hertig, A. T. Study of placenta accreta. *Surg., Gynec. & Obst.* 64:178-200, 1937.

7. Rademaker, L., Hansen, I. R., and La Rue, R. Placenta accreta. *Am. J. Surg.* 74:869-873, 1947.
8. Potter, M. G. Unusual case of placenta accreta discovered at cesarian section. *Am. J. Obst. & Gynec.* 35:1066, 1938.
9. Davidson, N. R. Placenta accreta. *J. Nat. M. A.* 36:90-92, 1944.
10. Hegar, A., and Maier, F. Cited by Irving and Hertig.[4]
11. Phaneuf, L. E. Placenta accreta, review of literature and report of 2 personal cases. *Surg., Gynec. & Obst.* 57:343-351, 1933.
12. Rutherford, R. N., and Hertig, A. T. Noninvolution of placental site. *Am. J. Obst. & Gynec.* 49:378-386, 1945.
13. Aaberg, M. E., and Reid, D. E. Manual removal of placenta. *Am. J. Obst. & Gynec.* 49:368-377, 1945.
14. Schumann, E. A. Pathology of third stage of labor, with especial reference to placental element. *M. Rec.* 151:381-384, 1940.
15. Wilens, I. Placenta accreta found at cesarian section for placenta previa. *Am. J. Surg.* 58:434-437, 1942.
16. Bosshardt, C. E. Placenta accreta: case report. *South. M. J.* 33: 1152-1155, 1940.
17. Anderson, H. Placenta accreta. *Am. J. Obst. & Gynec.* 42:545-547, 1941.
18. Conti, E. A. Placenta accreta. *Am. J. Surg.* 44:443-449, 1939.
19. Kaltreider, D. F. Placenta accreta. *Bull. Sch. Med. Univ. Maryland* 30:1-10, 1945.
20. Gemmell, A. A. Unusual case of adherent placenta treated in unorthodox manner. *J. Obst. Gynaec. Brit. Emp.* 54:213, 1947.
21. Jacobi, H. Removal of placenta accreta after one and one-half years retention. *Obst.-Gyn. Survey* 4:385, 1949.
22. Chisholm, W. N. Placenta praevia accreta. *J. Obst. & Gynaec. Brit. Emp.* 55:470-472, 1948.
23. Norman, S. P. Conservative treatment in placenta accreta: report of case in twin pregnancy. *New Eng. J. Med.* 240:60, 1949.
24. Shannon, W. F., and Dodenhoff, C. F. Placenta accreta found at cesarian section for placenta previa, with preservation of uterus. *Am. J. Obst. & Gynec.* 53:326-328, 1947.
25. Muir, J. C. Conservative treatment of placenta accreta with subsequent normal pregnancy. *Am. J. Obst. & Gynec.* 56:807, 1948.

THE USE OF ANTIBIOTICS AND VASODILATORS IN ATROPHIC RHINITIS (OZENA)*

Preliminary Report

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THE purpose of this report is to present a new method for the treatment of atrophic rhinitis with ozena, by combining the local use of streptomycin and other antibiotics with vasodilators. Various investigators in the past[1-3] have studied the local effects of vasodilator drugs in this disease. In 1938, Hnik[4] reported that histamine ionization resulted in reduction or elimination of the offensive odor and crusts and increased vascularization of the nasal mucosa. Recently,[5, 6] experiments with streptomycin in local and parenteral form have produced a striking disappearance of odor and the klebsiella organisms (Friedländer's bacillus), but a less appreciable effect on crust formations and no change in the atrophy. The significant though limited results obtained with these independently formulated methods of streptomycin and local-vasodilator therapy suggested a combined approach to the problem. In view of this it seemed more desirable to use several vasodilators, given orally and parenterally, in an effort to obtain more profound local effects on the vascular and neurotrophic changes typical of this disease. In addition to the use of specific antibiotic therapy certain vasodilators, namely, histamine, Priscoline and niacin, were studied with regard to their ability to increase the peripheral circulation of the nose.

A diagnosis of atrophic rhinitis with ozena was based on the presence of the following criteria: odor, crust formation, atrophy and gram-negative cultures showing Friedländer's bacillus, *E. coli*, *B. pyocyaneus* or *B. proteus*. The results in this report deal with the data of 13 particular cases observed over a period of one and one-half months to one year.

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Clinical Material

Four of the 13 patients selected for study were men and 9 were women, ranging in age from 27 to 73 years, with duration of symptoms from fifteen to fifty years. Four patients had been treated in the out-patient department over a fifteen-year period. Seven new patients were referred by the out-patient department and the remaining 2 patients were treated privately since the beginning of this work. Previous estrogenic therapy in the form of oily sprays (1-10,000; 1-20,000) had been received by 4 patients. Surgery was performed in 5 cases, followed by estrogen nasal sprays. Serum tests were negative in all cases.

Eight patients showed marked odor. It was slight in 3 and absent in 2. Although no odor could be detected objectively in 6 of the 11 patients on forced nasal expiration, it was nevertheless noticeable on the crusts removed by a cotton applicator. Crust formations distributed over the turbinates, nasopharynx and posterior surface of the soft palate were marked in 10 cases, moderate in 2 and slight in 1. Atrophy was marked in 11 patients and moderate in 2. Eleven showed complete anosmia, 2 partial. Nasal blockage and discharge were more or less present in all cases.

The bacteriologic findings consisted of pure gram-negative and mixed cultures, containing both gram-negative and gram-positive organisms.

Of 12 patients with sinus disease, x-ray evidence of nonsuppurative chronic sinus infection was present in 11, 1 showed active suppuration of a chronically infected right antrum and 1 was negative. The x-ray findings showed 4 with bilateral thickening and decalcification of the ethmoids, 1 with both

antra and ethmoids thickened, 1 with antra, ethmoids and sphenoids thickened, 3 with chronic bilateral pansinusitis, marked bone sclerosis and atrophy and 1 with cystic membrane of the right antrum. No retained pus was reported. One patient revealed 3 small ivory transplants in the septum and 1 showed a fluid level of pus in a chronic right antrum, with thickening of both ethmoids.

Methods

Cultures were taken in all cases before and during the course of treatment at three- and four-week intervals. After a positive report for the klebsiella or aerogenes organisms was obtained after the first clinical examination, the patient was started on treatment with the antibiotics and vasodilators in one of three ways as follows: streptomycin, histamine and niacin; streptomycin and Priscoline; streptomycin, penicillin and Priscoline. In addition, bacitracin and Gantrisin were employed with these combinations.

Streptomycin and penicillin were prescribed in aqueous concentrations to 20,000–30,000 units per cc. Instructions were given to use one-half dropperful (about 10,000 or 15,000 units) in each nostril for ten minutes 4 times daily, with the head in a low lateral position. Bacitracin was prescribed in aqueous concentration of 100 to 300 units per cc. Gantrisin was employed in 20 per cent aqueous concentration.

In general, the use of the particular antibiotics was indicated by predominant flora and response to the therapy. In mixed cultures of gram-positive and gram-negative bacilli, streptomycin was used with either penicillin or bacitracin. Bacitracin was usually given if penicillin reactions occurred. When gram-positive cultures appeared streptomycin was discontinued and penicillin or bacitracin was prescribed for the control of discharge. When gram-negative cultures persisted or reappeared, streptomycin and Gantrisin were employed either separately or in combination. When *B. proteus* was the predominant organism, Gantrisin was prescribed both locally and in tablet form (total daily dose, 4 gm.).

Preliminary sensitivity tests with histamine (histamine diphosphate 1 mg. per cc.) were carried out with dilutions of 1:100,000, 1:50,000 and 1:1000. Histamine diphosphate 1:5000 or 1:1000 were the maximal dilutions given subcutaneously in increasing dosage of 0.10 to 0.50 mg. twice weekly, depending on the flush reaction produced. Side reactions such as tightness of chest, abdominal or epigastric distress, headache, dizziness and weakness were watched for after the injections.

Priscoline was prescribed orally in dosage of 25 to 50 mg. 3 to 4 times a day. It is best to start with 25 mg. after meals, gradually increasing the dose and decreasing the interval until flushing occurs. As progressively increasing doses of Priscoline are given, patients are informed of side-reactions, which may occur as follows: flushing of the face and upper trunk; gradual warming of the extremities; increase of heart rate; slight rise or fall of blood pressure; temporary tingling and chilliness; increased peristalsis; and muscle twitching. Blood pressure was periodically measured. If signs of postural hypotension such as a fall in blood pressure, low-back pains or general weakness developed either the dosage was reduced or the drug was discontinued.

Niacin was prescribed in doses of 50 mg., from 4 to 6 tablets daily. The patient was prepared for the flushing and warmth of the face that rapidly follows the use of this drug.

In the management of nasal hygiene all patients were advised to discontinue nasal irrigations. Lamb's-wool plugs were prescribed to be inserted in each nostril 3 to 4 times hourly during the day, to stimulate secretion for the softening and easier elimination of crusts, before using nasal medication.

Clinical examinations were made weekly for the first two or three weeks of treatment, then once every two weeks. In these examinations an objective appraisal was made of the patient's odor on forced nasal expiration. If no odor was detected crusts or discharge was removed from the middle meati or sphenoethmoidal recesses of the nose and from the nasopharynx with a cotton applicator to determine its eventual presence. Patients were instructed to come without any treatment on the morning of their appointment in order to determine any change in objective findings.

An evaluation of the patient's sense of smell was made from the subjective history pertaining to such odors as coffee, lemon, various cooking spices and foods, perfumes, alcohol, gasoline and paint and an objective blindfold test for coffee, lemon and alcohol was made.

Results

Four of the 13 patients showed striking improvement and 6 showed significant improvement; 3 improved slightly. Patients classified as strikingly improved had a complete disappearance of odor, crust formations and organisms of the klebsiella group. In addition, local examination showed both an increase in moisture and circulatory filling of the turbinal mucous membrane and a partial return of the sense of smell. In the group with significant improvement there was a complete disappearance of odor and klebsiella organisms, a considerable elimination of crusts and some increase in moisture and turbinal filling. There was no return of the sense of smell. Those considered slightly improved showed complete or partial disappearance of odor and klebsiella organisms and a slight reduction in crusts but no change in the appearance of the mucosa.

In the strikingly improved group, 2 were treated with streptomycin, histamine and niacin, and two with streptomycin and Priscoline. Friedländer's bacillus disappeared in all these patients, although resistant *E. coli* and *B. proteus* remained. Of the 6 patients who showed significant improvement, 2 were treated with streptomycin and Priscoline and 4 with streptomycin, penicillin and Priscoline. In the majority of these patients, under both forms of treatment, the bacterial flora was changed to gram-positive organisms, with a complete disappearance of odor in all. In the slightly improved group of 3 patients, 1 was treated with streptomycin, histamine and niacin and 2 with streptomycin, penicillin and Priscoline. In the latter the bacterial flora was changed to gram-positive organisms, with a disappearance of odor in 1 and a significant reduction of the crusting in the others. Atrophy and anosmia were not affected. In the first patient, who discontinued treatment after one and a half months, odor and crusts were significantly reduced although atrophy remained the same. There was a partial return of the sense of smell (Table 1).

Two of 3 patients treated with streptomycin, histamine and niacin continued to show *E. coli* and *B. proteus* after eight and one-half months (Case 2) and five months (Case 3). Bacitracin alone and bacitracin with Gantrisin were used additionally in these cases.

Two of 4 patients treated with streptomycin and Priscoline showed a persistence of gram-negative organisms after four and one-half months (Case 5) and one year (Case 7). The latter, a twenty-seven-year-old woman, was the only patient to receive streptomycin parenterally; however, this drug was discontinued at the end of the first five weeks of treatment after the onset of vertigo and nausea. Except for a change in the bacterial flora to gram-positive organisms at the end of the eighth week, subsequent cultures showed resistant *E. coli* despite striking clinical improvement. The other two patients (Case 4 and Case 6) were free of gram-negative organisms after two and one-half months and five months, respectively.

In 2 of 6 patients treated with streptomycin, penicillin and Priscoline, gram-negative organisms persisted in one (Case 9) after six months and in the other (Case 13) at the end of six and one-half months. In both these cases Gantrisin was used additionally for resistant *B. proteus* with no change in the flora. In Case 9 bacitracin was used later instead of penicillin, because of the patient's sensitivity to penicillin. In the remaining 4 cases treated from five to eight and one-half months, a change to gram-positive flora occurred.

Results with streptomycin-histamine-niacin therapy are shown in 3 patients treated over a period of one and one-half to eight and one-half months (Table 1).

Case 1 was slightly improved, with a significant reduction of odor and crusts; atrophy remained the same and a return of the sense of smell for alcohol was noted at the end of four weeks. Case 2 was strikingly improved, with a complete disappearance of odor and crusts, and increased moisture and turbinal filling. There was a return of the sense of smell for alcohol. Case 3 showed striking improvement, with a complete disappearance of odor and crusts, a slight increase in turbinal filling and a partial return of the sense of smell for coffee.

Streptomycin and Priscoline therapy in four patients under active treatment from two and a half months to one year were as follows:

Case 4 was significantly improved, with complete disappearance of odor, although no effect on the crusts or atrophy was noted. There was partial return of the sense of smell for gas, oil and cooking odors. Case 5 showed striking improvement, with a complete disappearance of odor and crusts and increased turbinal filling. A partial return of the sense of smell was observed for alcohol and coffee. Case 6 was significantly improved, with a complete disappearance of odor, a marked reduction of crusts and good turbinal filling. Anosmia remained the same. Niacin and histamine were used additionally. Case 7 showed complete disappearance of odor and crusts and nearly normal filling of the turbinal structures. There was a remarkable improvement in the sense of smell. Streptomycin was discontinued at the end of the fifth month and Priscoline was the only medication taken since. Slight atrophy of the left inferior turbinate is still present. The left side of the nose has been consistently more resistant to treatment. This was the only case in the series in which streptomycin was given intramuscularly, in addition to its local use early in the course of treatment. Subsequent cultures have shown persistent *E. coli*, and sensitivity tests with streptomycin indicate that this organism is still nonresistant.

Results with six patients under active treatment with streptomycin, penicillin and Priscoline from three to eight and one-half months were as follows:

Case 8 showed complete disappearance of odor, marked reduction in crust formations and increased turbinal swelling. No effect on the anosmia was noted. Case 9, with no odor present before treatment, showed a marked reduction of crusts, only slight increase in turbinal filling and no change in the anosmia. Case 10, with no odor before treatment, was only slightly improved. There was a marked reduction of crusting but no change in the atrophy or sense of smell. In this patient, a seventy-three-year-old woman with irreversible atrophic changes showing airways nearly devoid of any turbinal structures, all medication was omitted because of an extensive allergic drug dermatitis, for which she has been under study in the allergy clinic. A recurrence of slight odor has since been

noted, although the massive crust formations and mucosal dryness involving almost the entire upper respiratory tract have been significantly lessened, both in character and amount, by the treatment that she had received up to that time. She can now more easily eliminate any crusts that may form without the necessity for nasal irrigations, which she had used for most of her life prior to treatment

TABLE 1. *Summary of Results with Combined Treatment.*

Case No.	Sex	Age	Sequence of Antibiotic Nasal Therapy (Aqueous)	Daily Dose	Culture		Last Report	Vasodilator Therapy	Daily Dose
					Before Treatment	During Treatment			mg.
1	M	35	Streptomycin (1½ mo.)	70,000 u.	*B. Fried.*	—	—	Niacin Histamine (2 wk.)	250 .35 (twice wk).
2	F	50	Streptomycin (5½ mo.) Penicillin (2 wk.) Bacitracin (1½ mo.) Streptomycin (1 mo.)	70,000 u. 70,000 u. 400 u. 70,000 u.	*B. Fried.*	Alpha-h. strept. H. *Staph. aur.*	*E. coli*	Priscoline (2 wk.) Histamine Niacin (3d mo.)	100 mg. 400 .30 (twice wk.)
3	F	42	Streptomycin (2½ mo.) Bacitracin (1½ mo.) Gantrisin 20% (2 wk.)	70,000 u. 400 u. 4 cc.	*B. Fried.* *B. pyocy.*	*Staph. alb.* *B. proteus*	*B. proteus*	Priscoline (1½ mo.) Histamine Niacin	100 .30 (twice wk.) 400
4	F	46	Streptomycin (2½ mo.)	70,000 u.	H. *Staph. aur.* *E. coli*	*B. parum.*	*B. parum.* *E. coli*	Priscoline	150
5	M	32	Streptomycin (4 wk.)	70,000 u.	H. *Staph. aur.* *E. coli*	—	*B. parum.*	Priscoline	100
6	F	32	Streptomycin (5 mo.)	70,000 u.	H. *Staph. aur.* *E. coli*	—	H. *Staph. aur.*	Priscoline Niacin	200 200
7	F	27	Streptomycin (2½ mo.)	70,000 u.	*E. coli* *B. Fried.*	*B. parum.* *H. influenzae*	Alpha-h. strept. *E. coli*	Priscoline Niacin	75-100 150
8	M	63	Streptomycin. Penicillin (1½ mo.) Bacitracin (2½ mo.)	70,000 u. 70,000 u. 400 u.	H. *Staph. aur.* *B. Fried.*	Alpha-h. strept.	H. *Staph. aur.*	Priscoline	100
9	M	32	Streptomycin Penicillin (1½ mo.) Streptomycin Gantrisin 20% (3 mo.)	70,000 u. 70,000 u. 70,000 u. 4 cc.	*B. proteus*	*E. coli*	*B. parum.* *E. coli*	Priscoline	200
10	F	73	Streptomycin Penicillin (5 mo.)	70,000 u. 70,000 u.	H. *Staph. aur.* *E. coli*	H. *Staph. aur.*	H. *Staph. aur.*	Priscoline (3½ mo.) Niacin (1 mo.)	100-200 300
11	F	51	Streptomycin Penicillin (3 mo.) Bacitracin (3 mo.)	70,000 u. 70,000 u. 400-1200 u.	*Parum. T3* *B. Fried.*	H. *Staph. aur.*	H. *Staph. aur.*	Priscoline Histamine Niacin	100-200 .50 300-400
12	F	57	Streptomycin Penicillin	70,000 u. 70,000 u.	*B. proteus*	—	—	Priscoline Niacin (2 mo.)	100 200
13	F	29	Streptomycin Penicillin (2 mo.) Gantrisin 20% (3 mo.) Streptomycin Gantrisin 20% (1½ mo.)	70,000 u. 70,000 u. 4 cc. 70,000-96,000 u. 4 cc.	Alpha-h. strept. H. *staph. aur.* *B. proteus*	*B. proteus*	*B. proteus*	Priscoline (3 mo.) Niacin (3 mo.)	125-200 200

with the lamb's-wool plugs. Case 11 was slightly improved, with a disappearance of odor. However, appearance of odor and a marked increase in turbinal filling. The crust formations were unaffected

TABLE 1 (*Concluded*).

CASE NO.	BEFORE TREATMENT				AFTER TREATMENT				ACTIVE TREATMENT	IMPROVEMENT	REMARKS
	ODOR	CRUST	ATROPHY	ANOSMIA	ODOR	CRUST	ATROPHY	ANOSMIA *no. of weeks*	*no. of months*		
1	++++	++++	++++	++++	++	+	++++	4 (alcohol)*	1½	Slight	
2	+	++	++++	++++	0	0	0	28 (alcohol)	8½	Striking	Antibiotics discontinued for 1 month after penicillin reaction of nasal and oral mucous membranes with reactivation of crusting and discharge
3	++++	+++	++++	++++	0	0	+++	4 (coffee)	5	Striking	Priscoline discontinued because of hypotensive symptoms
4	0	++	++++	+++	0	++	++++	6 (oil, gas, cooking)	2½	Significant	
5	+	++++	++++	++++	0	0	0	15 (alcohol, coffee)	4½	Striking	Gantrisin given orally (4 gm. daily) beginning with 4th month
6	++++	++++	++++	++++	0	+	+++	++++	5	Significant	
7	++++	++++	++++	++++	0	0	±	(Coffee, lemon)	12	Striking	Streptomycin also given intramuscularly (1 gr. daily for 6 weeks), discontinued with onset of vertigo. Histamine (1-1000 1.0 cc.) applied topically to sphenopalatine regions once during 7th and 8th weeks. In 9th week .05 cc. injected into left great sphenopalatine canal. Not observed for 6 weeks because of intercurrent illness
8	+++	++++	+++	++++	0	++	0	++++	5	Significant	Penicillin discontinued after 2nd week because of sensitivity rash of nasal and oral mucous membranes
9	±	±	++	++	0	±	+	++	4½	Significant	Gantrisin discontinued at end of 2½ months because of vomiting
10	0	++++	++++	++++	0	+	++++	++++	5	Slight	All medications discontinued in 5th month because of generalized skin rash diagnosed as dermatitis medicamentosa
11	+++	+++	++++	++++	0	+++	++++	++++	8½	Slight	
12	+++	++++	++++	+	0	++++	+	+	3	Significant	Penicillin discontinued after 1½ months because of nasal sensitivity reaction
13	+++	+++	++	++++	++	±	0	++++	6½	Significant	Penicillin discontinued after a month because of nasal sensitivity reaction. Priscoline omitted because of excessive aches and pains with low blood pressure

*Parentheses indicate odors for which the sense of smell returned.

rusts, atrophy and sense of smell were not affected. ase 12 showed significant improvement, with dis- and anosmia remained the same. Case 13 showed marked disappearance of crusts and rapid turbinal

filling response. Although there was a complete disappearance of odor at the end of six weeks, a mild recurrence was noted in the ninth week. The anosmia was not affected.

Discussion

Atrophic rhinitis has been classified in primary and secondary types. The primary form, commonly known as ozena, was first described by Fraenkel[7] in 1876. The predominant symptoms are a strong, permeating, offensive odor, extensive formations of green crust and atrophy of the turbinal structures. Anosmia is nearly always present. In the secondary type, which commonly occurs after long-standing suppurative disease of the sinuses or considerable intranasal surgical treatment, atrophic changes, crusting and anosmia are found without the peculiar feature of the ozena odor.

The true etiology of ozena has not yet been established; the most widely considered theories[8] have been the hereditary, anatomic, endocrine, neurotrophic and bacterial factors. The disease usually appears in early childhood or adolescence and is more common in females than in males.

The common pathologic changes seen in ozena[4] are: a transition from the columnar ciliated to a metaplastic stratified squamous epithelium; perivascular arteritis of the peripheral blood vessels; vascular atrophy; lymphocytic infiltration; and a progressive lacunar bone resorption of the turbinates. The gradual loss of the blood supply resulting from these vascular changes suggests a process closely resembling endarteritis obliterans.[8] Degenerative changes in the sphenopalatine ganglion are believed to account for the neurotrophic disturbances of the nasal mucosa and of the sense of smell.

The presence of odor, generally considered a constant finding in ozena, was variable in these studies and showed no definite correlation with the degree of crust formation and atrophy. In two cases in which blockage, crusting and atrophic changes were marked odor was found to be either barely detectable or entirely absent. These patients had routinely snuffed salt water or used nasal irrigations daily with various oily sprays for many years, but despite these hygienic precautions they still seemed acutely aware of either an offensive odor or an unpleasant taste. This was true of all the ozena patients in this series who have tried almost every form of conventional treatment, including estrogenic sprays, finally discarding them all and resorting to nasal irrigations or snuffing salt water. As a group these patients had become discouraged and hopeless after years of treatment without results, with the result that increasingly fewer of them are seen in hospital clinics or in private practice. The recent publicity given to streptomycin, however, has again stimulated their interest and renewed their hopes.

A comparison of the clinical results in the 13 cases showed 11 with complete and 2 with partial disappearance of odor after treatment. Since only 2 patients perceived no odor before treatment, this indicated that in 9 out of 11 patients it was completely eliminated. However, the constant fear that the odor might be detected by others served to channelize many deep-seated anxieties into a variety of psychosomatic symptoms. The patients' hope for a "cure" appeared to center mainly around its disappearance. Constant reassurance was necessary long before the reality of its elimination became accepted. In one patient (Case 7) this was particularly striking when, months after no odor could be detected, and despite her husband's corroboration, she was finally convinced when her child put his arms around her neck one morning and said, "Mummy, you don't smell any more."

It is difficult to explain why some patients showed a complete disappearance of odor, with either striking or significant clinical improvement, although cultures continued to show *E. coli* and *B. proteus*. This may suggest an immunity to gram-negative organisms in the habitat of the atrophic nose, whereas such organisms are not tolerated in the normal nose. It is also likely that local aqueous medication may not reach these organisms, — deeply imbedded as they are believed to be in the subepithelial layers of the mucous membrane, — in sufficient concentration, because of its lack of staying power. Higher concentrations of various antibiotics in powder form for local insufflation and oral use are now being investigated for more effective administration and dosage.

It is generally known that despite the excessive width of the nasal passages in atrophic rhinitis, patients nevertheless complain of marked blockage, which is due to the lack of resistance offered to air currents during nasal respiration.[9] In addition, the dried-out passageways covered with crusts and inspissated discharge tend to aggravate this condition still further. The daily use of nasal irrigations or douches had in general been the only resort of such patients, although followed by only temporary relief. It was difficult in the beginning to wean our patients from their daily routine by the use of lamb's-wool plugs. However, the relatively quick relief from the blockage, and the easier elimination of the crusts, particularly from the nasopharynx, were convincing proof to the patients of their effectiveness. The use of the plugs instead of irrigations also provided a more reliable method of appraisal of crust formations after treatment.

A correlation of length of treatment with clinical results indicated that significant improvement was noticeable after the third month of therapy. The response in patients who had had previous surgical treatment was much slower, as might be expected. Of 5 patients in this group 1 was unimproved

2 showed only slight improvement, 1 showed significant improvement and 1 was strikingly improved. These results support the now common opinion that sinus operations should not be performed in the presence of atrophic rhinitis.

Vasodilator therapy was generally well tolerated. Most patients noted an increase in their body warmth, — more particularly in the hands and feet, which formerly had always felt cold. The usual reaction after the histamine injection was a brief headache, nasal stuffiness and watery discharge, followed in some cases by a fairly rapid hyperemia of the nasal mucosa with a sensation of nasal warmth. When Priscoline was taken later this effect appeared to be intensified, lasting for about one hour. In 1 case not included in this series an irregularity of the menses was observed with this drug, with a prompt return to normal after the dosage was reduced. It was increasingly evident that the use of the vasodilator drugs proved more effective in combination than singly in promoting the circulatory response of the nasal mucosa, as well as its secretory function. The obvious increase in the erectile-tissue filling of the inferior turbinates and in the moisture content of the nose and the partial return of the sense of smell, together with the local effectiveness of antibiotic therapy, were an indication of permeability. This suggests that even in the advanced atrophic nose cellular changes may not be entirely irreversible or outside the limits of functional restoration. Among those who have worked with this problem it is well understood that a long period of observation is necessary before final results can be truly evaluated.

Summary and Conclusions

A new method for the treatment of atrophic rhinitis (ozena) with streptomycin and other antibiotics combined with certain vasodilators such as histamine, Priscoline and niacin is presented. Their local, oral and parenteral use is described.

The clinical and bacteriologic data of 13 patients observed under treatment at the Massachusetts Eye and Ear Infirmary over periods of one and one-half months to one year form the basis of this preliminary report.

The end results in the 13 cases treated show 4 patients with striking improvement and 6 significantly and 3 slightly improved.

The data thus far obtained suggest that the combined use of properly selected antibiotics and vasodilators can effectively eliminate odor and crusts and promote a reversal of the regressive changes in atrophic rhinitis with ozena.

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References

1. Angelescu, G. L'ozène et l'acétylcholine (avec 6 observations nouvelles). *Ann. d'oto-laryng.* Pp. 669-674, 1932.
2. Halphen, E., and Djiropoulos. Traitement de l'ozène par l'association de la bactériophagie et de la vasodilatation médicamenteuse ou radiothérapeutique. *Presse méd.* 41:190-192, 1933.
3. Tello, A. Contribución al estudio de la vía intradérmica en el tratamiento de las algias esenciales y de algunas manifestaciones de ozena. Histamina, tuberculina y agua destilada. *Rev. méd. de Chile* 67:136-140, 1939.
4. Hnik, J. Histamine ionization in therapy of atrophic rhinitis and ozena. *Casop. lék. cesk.* 77:681-685, 1938.
5. Simonton, K. M. Streptomycin treatment of ozena. *Proc. Staff Mert., Mayo Clin.* 24:337-340, 1949.
6. Thornell, W. C. Ozena: streptomycin and nitrofurasone therapy. *Arch. Otolaryng.* 52:96-103, 1950.
7. Fraenkel, B. Cited by Wachsberger, A. Surgical correction of atrophy in ozena. *S. Clin. North America* 18:487-498, 1938.
8. Cullom, M. M. Cited by Thornell, W. C. Atrophic rhinitis in plastic surgery. *Laryngoscope* 50:510-519, 1940.
9. Sternstein, H. J. Nasal obstruction in adult: quantitative study. *Arch. Otolaryng.* 25:442-448, 1937.

THE USE OF ACTH IN ACUTE VIRAL HEPATITIS*

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THE reports of the effectiveness of ACTH against many diseases resistant to all previous therapeutic measures[1,2] suggested a trial of ACTH in the management of acute viral hepatitis. The following is a report of the investigation of the use of ACTH in treatment of viral hepatitis at the Hepatitis Center, Ninety-Eighth General Hospital, U. S. Zone of Occupation, Germany.

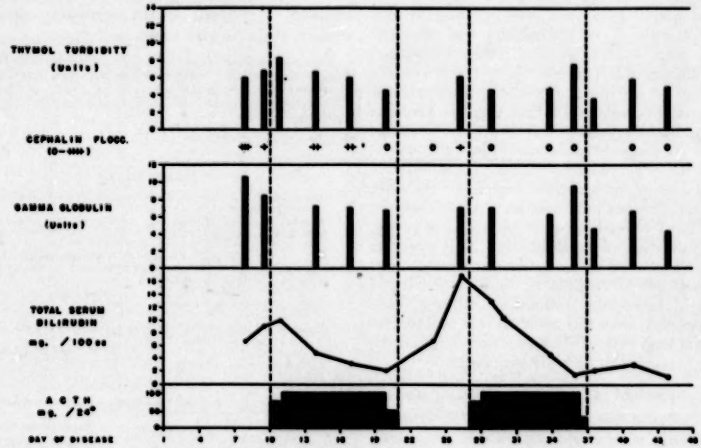

FIGURE 1. *Effect of ACTH on the Course of Viral Hepatitis in Patient R. T.*

At this center over 4000 cases of viral hepatitis have been treated during the past three years, 1947–1950.[3]

MATERIALS AND METHODS

The patients studied in this investigation were 5 male enlisted personnel of the United States Army of Occupation in Germany who were admitted to the hepatitis wards of the Ninety-Eighth General Hospital within the first eight days of the onset of viral hepatitis. It is possible that some of these cases were examples of homologous serum hepatitis, but, in view of the fact that there are at present no means of clinical differentiation of infectious hepatitis and serum hepatitis, the cases have all been classified as viral hepatitis. The diagnosis was made on the basis of characteristic symptoms and signs accompanied by consistent deflection of appropriate tests of hepatic function. The 5 patients studied were jaundiced at the time of admission; the subsequent course of disease was mild or moderately severe. All patients were under twenty-five years of age.

The patients were examined daily and observations made concerning pertinent symptoms and signs of disease. Laboratory tests of liver function were performed on admission and twice a week throughout the period of hospitalization. A regimen of low-salt diet and the daily charting of weight, blood pressure, intake and output and eosinophil count[4] were instituted prior to administration of ACTH. Complete blood counts, urinalyses and glucose-tolerance tests were carried out before

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treatment and weekly thereafter. The urine was examined daily for glucose.

ACTH was administered intramuscularly (25 mg. every six hours) and was discontinued abruptly. The total dose per patient varied between 825 mg. and 1925 mg.

Except for the administration of ACTH the patients followed a standard management routine. The diet contained 4200 calories and consisted of 190 gm. of protein, 607 gm. of carbohydrate and 114 gm. of fat, supplemented with vitamins and brewer's yeast but with salt intake restricted. All patients remained in bed, although allowed to walk to the bathroom, until all symptoms and signs of hepatitis had disappeared and the retention of bromsulfalein in the blood measured 6.0 per cent or less. They were then allowed to be ambulatory for one week. After this, if there was no evidence of relapse, either clinically or as determined by tests of hepatic function, they were discharged from the hospital either to duty or to a convalescent center.

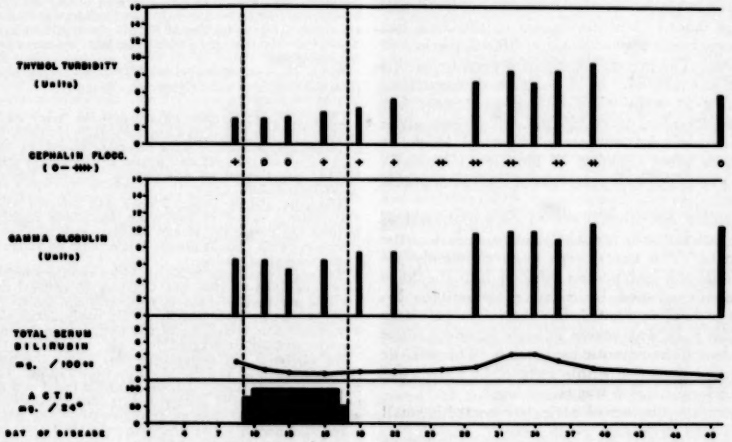

FIGURE 2. *Effect of ACTH on the Course of Viral Hepatitis in Patient A. B.*

RESULTS

Appropriate response of the eosinophils to ACTH administration was seen in each instance.

The most striking result was the prompt return of appetite and energy. Anorexia diminished rapidly and voracious appetite was manifested. The patients felt so well that it became difficult to maintain bed rest. Any pruritus disappeared during treatment. Although jaundice receded during treatment, no definite change in liver size or tenderness was found.

A definite effect on the level of the serum bilirubin was noted. In all cases serum-bilirubin levels showed a prompt fall, and on cessation of ACTH therapy 2 patients exhibited a significant rise in serum-bilirubin concentration (Fig. 1 and 2). The cephalin-flocculation and thymol-turbidity tests did not follow so clear a trend. However, there were indications that ACTH was a causative factor in the return of these tests to normal. Gamma-globulin levels[5] appeared to be slightly depressed by the action of ACTH, but this effect likewise was not conclusively demonstrated. Bromsulfalein retention (5 mg. per kg. of body weight), which was determined after the one-minute serum bilirubin had fallen to 0.4 mg. per 100 cc., was abnormal at first examination in all cases.

Two patients (R. T. and A. B.) experienced clinical relapse on withdrawal of ACTH (Fig. 1 and 2). In both instances the relapse was more severe than the initial episode. Anorexia, nausea and abdominal cramps were accompanied by a rise in the total and one-minute serum bilirubin and a return to abnormal reaction of the cephalin-flocculation and thymol-turbidity tests. One of these patients (R. T.) was again given ACTH; within six hours nausea and abdominal discomfort vanished, his appetite became better and general improvement was noted. By the seventy-second hour he was energetic and cheerful, and his total serum bilirubin had fallen markedly. When ACTH was withdrawn

for the second time this patient again exhibited a rise in serum bilirubin, but it was of minor degree (Fig. 1). The other patient was treated routinely without ACTH and remitted spontaneously but without dramatic suddenness (Fig. 2).

Untoward effects were noted in all 5 patients. Ascites, sacral edema, moon face and acne developed in 4 patients. Ascites and sacral edema disappeared with the diuresis that accompanied hormone withdrawal, but the rounded facies and acne persisted a few days longer.

Rise in systolic blood pressure to a level of over 140 was observed in all patients and a diastolic blood pressure of 90 or more was noted in 4 patients. One patient (P. A.) exhibited significant hypertension one month after withdrawal of the drug but was normotensive two months after cessation of treatment. The pretreatment blood pressure of this patient was 138/84. All 5 patients demonstrated glycosuria at some time during treatment, but glucose-tolerance curves (25 gm. of glucose given intravenously) did not show abnormal levels at two hours after injection of glucose. Glycosuria ceased promptly with cessation of ACTH administration.

A striking symptom observed on withdrawal of ACTH was the occurrence of joint pains in 4 of the 5 patients. The knees were most commonly involved; in one instance an effusion into the knee joint was confirmed by x-ray examination. No redness or heat was noted, but the joints were tender. The pain was severe enough in one patient (J. B.) to require narcotic medication. This patient experienced remission within forty-eight hours after ACTH administration was reinstituted.

Because the number of patients reported is small detailed case records are given below.

Case Reports

Case 1. P. A., a nineteen-year-old infantryman, was admitted to the Hepatitis Center on May 11, 1950, because of scleral icterus. He was well until four days before admission, when fatigue, dark urine, postprandial nausea and anorexia appeared. For three days prior to entry intermittent frontal headache and dull epigastric pain were noted; on the day of admission jaundice was noticed.

He drank 5 or 6 bottles of beer weekly; he had never been in the tropics and had never been exposed to hepatotoxic chemicals. He had had no previous jaundice and had been given no needle punctures in the past six months. The rest of the personal, past and family histories was generally unremarkable.

On admission the temperature was 98.2°F., the pulse 64, the respirations 20 and the blood pressure 138/84. Icterus of the skin and scleras was seen. The heart and lungs were normal. The abdomen was flat and muscular; the liver extended only to the costal margin and was slightly tender; the spleen was not palpable. The remainder of the physical examination was within normal limits.

Examination of the blood revealed a hemoglobin of 15.3 gm. and a white-cell count of 10,750, with 59 per cent neutrophils, 29 per cent lymphocytes, 11 per cent monocytes and 1 per cent eosinophils. Except for bilirubinuria the admission urinalysis was within normal limits. Chest x-ray films and a cardiolipin test were negative. Liver-function tests revealed a total serum bilirubin of 6.3 mg. per 100 cc., +++ cephalin flocculation, a thymol turbidity of 14 units and a gamma-globulin turbidity of 16.5 units.

On the seventh day the patient was started on ACTH, — 25 mg. 4 times daily, by intramuscular injection. His serum bilirubinuria declined to a concentration of 1.26 mg. per 100 cc. in twelve days, and his appetite became enormous. The appearance of a full, rounded, plethoric "moon" facies on the eleventh day of ACTH administration was striking. After 1675 mg. of ACTH had been administered in eighteen days the drug was discontinued because of the appearance of sacral edema, significant diastolic hypertension and an acneform eruption over the upper anterior chest and back first seen on the eighteenth day of treatment. From the thirteenth to eighteenth day of treatment ascites was noted.

Approximately sixteen hours after cessation of ACTH the patient experienced bilateral aching pains in both knees that interfered with sleep but spontaneously disappeared in forty-eight hours. No objective signs of bone or joint disease were apparent on examination. The sacral edema cleared rapidly, as did the rounded facies, but acne of the chest persisted for three weeks after the cessation of medication. Diastolic hypertension, which appeared during ACTH treatment, persisted for one month after withdrawal of the drug. On about the fifteenth day of ACTH therapy, and again ten days after cessation, the patient had brief epistaxes from the left nares.

Serial electrocardiograms made before, during and after treatment failed to show significant changes.

Case 2. J. L., a twenty-three-year-old Army clerk, was admitted to the Hepatitis Center on May 17, 1950, because of icteric scleras. Three days before admission he observed dark urine; on the next day icterus of the scleras appeared. He had experienced no other symptoms, and felt entirely well on admission.

The past history included acne and infected sebaceous cysts over a period of five years, for which penicillin injections had been given 58 and approximately 80 days before the onset of his present illness. There were no active lesions at the time of admission.

The patient had been in North Africa and the South Pacific area from 1944 to 1946 but had had no tropical diseases. He had not been exposed to hepatoxic chemicals. He had never previously been jaundiced. He rarely drank alcoholic beverages. The remainder of the past, personal and family histories was not remarkable.

On admission the temperature was 99°F., the pulse 80, the respirations 18 and the blood pressure 120/80. The skin and scleras were slightly jaundiced. Mild facial and cervical pitting from acne and scattered scars from incisions of cysts were noted. There was no telangiectasia. The heart and lungs were normal. The liver was palpable 1 fingerbreadth below the costal margin and was slightly tender, but the spleen was not palpable. The remainder of the physical examination was within normal limits.

Examination of the blood revealed a hemoglobin of 14.8 gm. and a white-cell count of 3850, with 52 per cent neutrophils, 40 per cent lymphocytes, 3 per cent monocytes and 5 per cent eosinophils. Urinalysis was within normal limits and a cardiolipin test was negative. Liver-function tests demonstrated a total serum bilirubin of 2.2 mg. per 100 cc., ++ cephalin flocculation, a thymol turbidity of 8 units and a gamma-globulin turbidity of 10 units.

On the eighth day the patient was started on ACTH, 25 mg. given intramuscularly 5 times. On this regimen his appetite and intake were greater than ever before in his life and the serum-bilirubin concentration fell to normal within four days. He experienced exceptional well-being. On the seventh day fullness of the face first appeared; this progressed. On the eleventh day he began to cough up small amounts of frothy white sputum, without dyspnea, orthopnea or pulmonary rales. On the twelfth day significant diastolic hypertension developed. On the thirteenth day, after 1225 mg. of ACTH had been given, the drug was withdrawn on the appearance of ascites and sacral edema. This increased transiently and disappeared after ten days.

The patient had no joint, bone or muscle aches in the post-therapy period. In spite of diuresis his weight did not return to the pretreatment level, and his face remained full and rounded. It was clinically apparent that he had gained weight, probably because of the continued excellence of his appetite. Serial electrocardiograms made during the period of hospitalization showed no significant changes. He was discharged to duty on the thirty-ninth hospital day.

A repeat examination on the sixty-first day after the onset of the disease revealed normal findings except for persistent hepatic enlargement with slight tenderness.

Case 3 (Figure 2). A. B., a twenty-year-old radio operator, was transferred to the Hepatitis Center on May 22 with a diagnosis of viral hepatitis. Seven days earlier nausea, anorexia, dark urine, light-colored stools, chilliness and fever had appeared during the course of three days. Four days before transfer icterus was noted, and he was admitted to the 15th Evacuation Hospital. There jaundice and epigastric tenderness without hepatomegaly were noted, with a total serum bilirubin of 4.13 mg. and a 1-minute serum bilirubin of 1/72 mg. per 100 cc. On admission to the Hepatitis Center only mild anorexia, bilirubinuria and alcoholic stools persisted.

The patient had scarlet fever at the age of seven without remembered sequelae. He had never had acute rheumatic fever. Ninety days before the onset of the present illness he had had acute tonsillitis, for which repeated injections of aqueous penicillin were given. Three weeks prior to the onset of hepatitis he had painted woodwork with white lead paint; after this he developed a rash on his hands that lasted for three days, but no gastrointestinal symptoms or jaundice was noted at that time. He could not recall any exposure to possible hepatotoxins. He drank no alcoholic beverages. The remainder of his personal and past history was negative.

On admission the patient presented mild jaundice and a few widely scattered acneform lesions of the face and back. The temperature was 99°F., the pulse 60, the respirations 16 and the blood pressure 108/64. The heart was not enlarged. Regular sinus rhythm was present, and the sounds were of good quality. A Grade I systolic murmur was heard in the apical and aortic regions. The lungs were clear to percussion and auscultation. The liver did not extend below the costal margin but was slightly tender. The spleen was not palpable.

Examination of the blood revealed a hemoglobin of 12.2 gm. and a white-cell count of 4050, with 45 per cent neutrophils, 4 per cent eosinophils, 2 per cent basophils, 7 per cent monocytes and 42 per cent lymphocytes. The urinalysis was normal. The cardiolipin test was negative. Admission photofluorogram of the chest was entirely normal.

An initial battery of chemical tests of liver function was obtained (Fig. 2), and on the ninth day the patient was started on ACTH. He experienced only moderate well-being during medication, but his bilirubinemia declined. On the ninth day of treatment his heart seemed slightly enlarged, and the murmurs had increased in intensity. At this time the blood pressure was 135/90 and the neck veins were distended. Medication was stopped because of this evidence of cardiac embarrassment. The patient received 825 mg. of ACTH in ten days. During the course of treatment his weight remained constant, due to loss of tissue during storage of fluid. Three days after cessation of ACTH he had diuresed 3.0 kg. After a 24-hour latent period the patient experienced mild aching in his knees, without abnormal physical findings; this lasted less than a day.

Four days after the end of the course of treatment he began to note intermittent symptoms of mild nature similar to those at the onset of his disease: anorexia, epigastric cramps and later bilirubinuria and acholic stools. Five days after withdrawal of ACTH there was an appreciable increase in the serum bilirubin. By the end of the second week after cessation of ACTH therapy all the tests were more abnormal, and the bilirubinemia exceeded that on admission. At the peak of jaundice the symptoms abated, and the patient then gradually recovered.

Serial electrocardiographic tracings failed to disclose significant changes, and cardiac fluoroscopy was normal.

Case 4 (Fig. 1). R. T., a nineteen-year-old military policeman, was admitted to the Hepatitis Center on May 23, 1950, because of jaundice. Seven days earlier he had noted epigastric fullness, which was rapidly followed by persistent anorexia, nausea, headache, pruritus and dark-colored urine. Two days before admission he noticed scleral icterus.

Four months prior to entry the patient had been treated for seropositive primary syphilis with 6,000,000 units of procaine penicillin. He had had needle punctures 109 and 87 days before the onset of symptoms. He had been a "heavy" beer and whisky drinker for two years. He had no history of prior jaundice and had not been exposed to hepatotoxic chemicals.

On admission the temperature was 98.6°F., the pulse 54, the respirations 18 and the blood pressure 120/80. There was icterus of skin and scleras, and a minimal chronic acneform eruption overlying the sternum. The skin was otherwise clear, without telangiectasia. The heart and lungs were normal. The liver was percussed 1 fingerbreadth below the right costal margin, but an edge was not felt. The spleen was not felt. The remainder of the physical examination was within normal limits.

Examination of the blood revealed a hemoglobin of 14.8 gm. and a white-cell count of 4150, with 50 per cent neutrophils, 37 per cent lymphocytes, 8 per cent monocytes, 4 per cent eosinophils and 1 per cent basophils. Urinalysis was within normal limits and a cardiolipin test was negative.

Two sets of liver-function tests were obtained prior to administration of ACTH on the fourth hospital day. Four days later the patient's anorexia had disappeared, and his appetite was enormous. Pruritus ceased on the sixth day of treatment. Intermittent midabdominal pains and hepatic tenderness continued. The fall in the bilirubin during this period is shown in Figure 1. During the latter days of ACTH administration a pulmonic systolic murmur, rounded full facies and sacral edema appeared.

On the twelfth day of ACTH medication was stopped because of the development of ascites. Within fourteen hours arthralgia appeared in the wrists, elbows, ankles and knees, without effusion or other local finding except tenderness. Twenty-four hours later the pain encompassed the whole of the lower extremities and the left shoulder girdle, with tenderness of muscle, bone and joint. The pain in these regions was not changed during movement but was considerably increased after activity. After eighty hours these extremity pains disappeared.

The second day after withdrawal of ACTH a small right-sided epistaxis occurred.

Approximately forty-eight hours after cessation of ACTH the original symptoms recurred. Pruritus, anorexia, nausea, vomiting, lethargy and epigastric cramps became prominent, and a striking increase in the total serum bilirubin from 2.02 to 16.70 mg. per 100 cc. occurred in seven days. During this period a marked diuresis occurred (with a weight loss of 7.3 kg.) and the rounded face reverted to normal. The indolent anterior-thoracic acne became active the day after withdrawal of ACTH, and a florid acneform eruption appeared and steadily worsened. On the seventh day after withdrawal the patient appeared acutely ill. He was deeply jaundiced and suffered severe pruritus. Innumerable petechial hemorrhages appeared in the areas where he had scratched himself. A tourniquet test was negative after three minutes. Bleeding time was two minutes and venous clotting time five minutes (Lee–White method). The platelet count was 127,680.

On the seventh day after cessation of ACTH because of the severe relapse, ACTH was again initiated in the same dosage as before. Within six hours nausea and abdominal discomfort vanished, the patient's appetite increased and he felt generally improved. By the seventy-second hour he was energetic and cheerful, his appetite was enormous and his total serum bilirubin had fallen to 10.40 mg. per 100 cc., a drop of 6.30 mg. During treatment pruritus slowly disappeared and the acne healed. Mild purpura in scratched areas continued to appear for seven days, and small right epistaxes occurred on the eighth and ninth days of the second course of treatment. Moderate tenderness of the lower thirds of both tibias was present from the seventh day of therapy until cessation of ACTH. Variable sinus bradycardia to a recorded low of 38 appeared in the latter half of the therapeutic trial without other physical or electrocardiographic abnormality. Rapidly accumulating ascites and mild somnolence on the ninth and tenth days prompted discontinuation of the drug. On the tenth day the total serum bilirubin had fallen to 1.68 mg.

Immediately after cessation of treatment a similar but milder relapse ensued. Pruritus and jaundice (maximum serum bilirubin 3.04 mg.) again occurred. The hyperbilirubinemia slowly declined over a sixteen-day period. His subsequent course was one of slow convalescence with elevated bromsulfalein-retention values.

Serial electrocardiographic tracings throughout the hospitalization revealed no significant findings other than sinus bradycardia during the second period of treatment with ACTH.

Case 5. J. B., a twenty-two-year-old tank driver, entered the Hepatitis Center on May 23, 1950, because icteric scleras had been noted three days previously. For the two days prior to entry he had noted dark urine and light stools but had had no other symptoms and felt entirely well.

The past history indicated no relevant illnesses. He drank 20 to 25 bottles of beer weekly; he had never been in the tropics and had not been exposed to hepatotoxic chemicals; he had had no needle punctures in the preceding six months. Personal and family histories were negative.

On examination jaundice of skin and scleras was seen. The temperature was 98°F., the pulse 68, the respirations 18 and the blood pressure 112/68. The heart and lungs were normal. The abdomen was flat and muscular. The liver could be percussed 2 fingerbreadths below the right costal margin but could not be felt. The rest of the physical examination was within normal limits.

Examination of the blood disclosed a hemoglobin of 13.2 gm. and a white-cell count of 4350, with 57 per cent neutrophils, 24 per cent lymphocytes, 7 per cent monocytes, 11 per cent eosinophils and 1 per cent basophils. Urinalysis was within normal limits, as was a chest x-ray film. Laboratory tests of liver function revealed a total serum-bilirubin concentration of 4.9 mg., negative-cephalin flocculation, a thymol turbidity of 3.75 units and a gamma-globulin turbidity of 6.25 units.

On the fifth day administration of ACTH was begun. The patient received a total of 975 mg. in eleven days, during which time he felt extremely well. His appetite was enormous and he ate far more than ever before in his life. The serum bilirubin concentration fell rapidly and was normal within nine days of treatment. Hypertension, a plethoric rounded facies and sacral edema were associated with drug administration. Engorged neck veins and a soft blowing pulmonic systolic murmur were first noted after the tenth day of treatment. Ascites appeared on the eleventh day of ACTH, and the medication was stopped.

Approximately sixteen hours after the last dose the patient suffered excruciating leg pains, which started at the dorsa of the feet and radiated to the knees. Twenty-four hours later a definite small effusion was detected in the left knee joint and confirmed by x-ray examination. The right knee was slightly less tender, but no definite signs of effusion were seen there. Neither extremity demonstrated local heat or redness, and pain was not greatly increased by motion. In the first twenty-four hours of pain a total of 2.1 gm. of aspirin and 0.18 gm. of codeine were ineffective, and the patient required 2 parenteral 100-mg. doses of Demerol for relief.

A minimal acneform eruption limited to the anterior central thoracic region first appeared on the day after cessation of ACTH.

To elucidate further the relation of joint pains to the ACTH treatment in this patient, the drug was reinstituted in the same dosage schedule 53 hours after cessation of the first course. Four and one-half hours later, when the eosinophil count was reduced by 46 per cent, the pain had not remitted. For twenty-four hours after the drug was reinstituted his pain was still severe, but thereafter it improved; the effusion disappeared, and by the forty-ninth hour the patient had again become asymptomatic, with no evidence of joint disease on examination. On the second day after reinstitution of therapy his appetite returned to the level of the first course, his face became fatter and more plethoric than it had been in the short period of drug withdrawal, ascites began to increase and he again experienced exceptional well-being. The chest eruption increased greatly during the second course. A small unilateral epistaxis occurred on the fourth day of treatment.

After 675 mg. had been given in eight days the drug was again stopped, as at that time there was no clinical or laboratory evidence of hepatitis. Twenty-four hours later a definite small effusion was present in the right knee, with mild pain, but the other bones and joints were entirely symptom-free. The effusion was no longer detectable at twenty-four hours, but mild pain persisted, gradually involving the left knee until the fourth post-treatment day, when severe pain again appeared in the right knee, without effusion. This lasted twenty-two hours and then disappeared completely.

The anterior-thoracic acne, which had become marked during the second course of treatment, progressively involuted after medication was stopped. On the second post-treatment day a mild folliculitis appeared at the hairline that persisted for two days. The plethoric full facies gradually regressed after cessation of ACTH therapy.

Hepatic-function tests showed a progressive return to normal without evidence of relapse.

Serial electrocardiograms made during the period of hospitalization showed no significant changes.

Comment

The apparently beneficial result produced by ACTH in the treatment of acute viral hepatitis as described in this study is in agreement with the findings of Thorn and others[2] in the treatment of a case of homologous serum hepatitis. However, the present report is at variance with that of Bluemle and his co-workers,[6] in which no improvement attributable to ACTH was noted in 2 cases of acute viral hepatitis. In our investigation apparently good results were seen in all 5 cases. It is not our intention to attribute the recovery of these patients to ACTH administration, but the course of disease in the patient R. T., in whom remission was associated with ACTH administration and relapse with ACTH withdrawal on two occasions, points to a beneficial effect of ACTH therapy in acute viral hepatitis.

The occurrence of migrating arthralgia concomitant with hormone withdrawal in 4 of the patients requires comment. The abrupt discontinuance of ACTH was most probably followed by a period of adrenal insufficiency; during this period the joint and muscle pain developed. The diuresis occurring during a time of relative adrenocortical hypofunction may have produced a sodium loss that resulted in muscle cramps, but the presence of joint effusion in patient J. B. suggested that more than electrolyte imbalance was needed to explain the symptoms. One of the patients (A.B.) probably had a pre-existing rheumatic diathesis, but the other 3 patients who presented symptoms of arthralgia exhibited no evidence, from history or physical examination, of rheumatic fever or rheumatoid arthritis.

Sensitization to ACTH should be mentioned as a possible cause of the arthralgia. The development of symptoms could have been masked by the inciting agent itself (ACTH); they then might have made their appearance when the drug was withdrawn.

Summary

Five patients with acute viral hepatitis received 100 mg. of ACTH daily in 4 divided doses for periods ranging between nine and twenty-one days. Marked symptomatic improvement occurred promptly and

was associated in all instances with a falling serum-bilirubin concentration.

On withdrawal of ACTH arthralgia developed in 4 patients, 1 of whom demonstrated joint effusion.

Other untoward effects seen were glycosuria, hypertension, edema, ascites, "moon" face and acne.

Addendum

Since this paper was written Sborov and his associates have reported on the slow intravenous administration of smaller amounts of ACTH to patients with viral hepatitis.[7] The results appeared favorable and the side-reactions few.

References

1. *Proceedings of the First Clinical ACTH Conference.* Edited by J. R. Mote. 607 pp. Philadelphia: The Blakiston Company, 1950.
2. Thorn, G. W., et al. Clinical usefulness of ACTH and cortisone. *New Eng. J. Med.* 242:783-793, 824-834, and 865-872, 1950.
3. Symposium on viral hepatitis. Edited by W. P. Havens, Jr. *Am. J. Med.* 8:559-622, 1950.
4. Randolph, T. B. Blood studies in allergy: direct counting chamber determination of eosinophils by propylene glycol aqueous strains. *J. Allergy* 15:89-96, 1944.
5. Kunkel, H. G. Estimation of alterations of serum gamma globulin by a turbidimetric technique. *Proc. Soc. Exper. Biol. & Med.* 66: 217-224, 1947.
6. Bluemle, L. N., Jr., et al. Use of adrenocorticotrophic hormone in chronic liver disease (three cases). In *Proceedings of the First Clinical ACTH Conference.* Edited by J. R. Mote. 607 pp. Philadelphia: The Blakiston Company, 1950. Pp. 505-508.
7. Sborov, V. M. *Proceedings of the Second Clinical ACTH Conference.* Edited by J. R. Mote. Vol. I. Philadelphia: The Blakiston Company, 1951. Pp. 381-384.

FALSE-POSITIVE TEST FOR PHEOCHROMOCYTOMA WITH AN "ADRENOLYTIC" COMPOUND*

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A NUMBER of pharmacologic tests have been devised to aid in the difficult clinical diagnosis of pheochromocytoma, particularly when it is accompanied by persistent hypertension.[1] Of these, the intravenous administration of benzodioxane (2-[1-piperidylmethyl]-1, 4-benzodioxane), though not infallible,[1-3] appears to be most specific.[4] In a series of 61 patients with hypertension who were tested with benzodioxane, 1 showed a reduction in blood pressure; that patient had a pheochromocytoma.[5] However, this agent may occasionally cause alarming pressor responses in essential hypertension,[6, 7] and reports have appeared of patients with pheochromocytomas who responded to benzodioxane with a rise in blood pressure.[1, 8]

Spear and Griswald[9] reported the first case of a fall in blood pressure after the administration of dibenamine (N,N-dibenzyl-β-chloroethylamine) to a patient who proved at operation to have a pheochromocytoma. Recently case reports have appeared in which both benzodioxane and dibenamine were effective in lowering the blood pressure to normal in a patient subsequently proved to have a pheochromocytoma.[10, 11]

The availability of an additional pharmacologic test would be most useful. It becomes important, therefore, to establish whether a fall in blood pressure after administration of dibenamine or its congeners is indeed diagnostic, or even presumptive evidence, of a pheochromocytoma.

A hypotensive response from dibenamine in 6 of a group of 20 hypertensive patients was reported by Haimovici and Medinets.[12] Hecht and Anderson[13] noted a fall in the supine blood pressures of two out of ten hypertensive patients after dibenamine. Wunsch and others[14] reported that dibenamine caused a fall in the supine blood pressures of all of a group of 14 patients with fixed hypertension, 10 of them in the malignant phase. Haimovici and Medinets,[12] however, reported no fall in 2 patients with malignant hypertension. Such high percen-

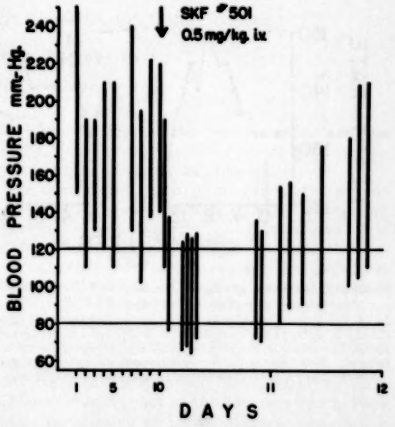

Figure 1. *Response of Blood Pressure to an Intravenous Injection of 26 Mg. of SKF No. 501.*

The blood pressure was normal for one day and rose during the second day to control levels.

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tages of positive responses far exceed any likely incidence of pheochromocytoma. However, if an agent with adrenolytic properties has caused a fall in the supine blood pressure in a hypertensive patient, even failure to find a tumor after exploration of both adrenal glands would not eliminate the possibility that a chromaffin tumor was present, for at least 15 per cent of these tumors are extra-adrenal.[4]

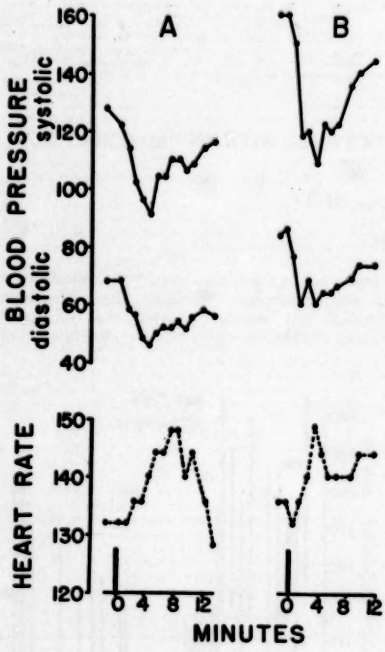

FIGURE 2. *Response of Blood Pressure and Heart Rate to Epinephrine after Administration of SKF No. 501.*
In A, five hours after administration of the "adrenolytic" agent, 0.2 mg. of epinephrine (adrenalin) was injected subcutaneously. In B, twenty-three hours later, 0.1 mg. of epinephrine was injected. Both show a fall in systolic and diastolic blood pressure. The epinephrine-induced tachycardia is unaffected.

In the case reported herein, adrenergic blockade was produced with SKF No. 501 (N-9-fluorenyl, N-ethyl-β-chloroethylamine), a congener of dibenamine.[15] The dose used was 0.5 mg. per kg., which is comparable to 5 mg. per kg. of dibenamine in adrenergic blocking action.[16] Completeness of adrenergic blockade was tested by the response to injections of epinephrine.

CASE REPORT

A 58-year-old woman (R. F. No. M1723), was admitted to the hospital because of asphasia of 3 weeks' duration. She had had hypertension for 10 years and had taken digitalis and nitroglycerin for 3 years. Difficulty in speech appeared 1 month before entry and in the following week progressed to complete aphasia, with inability to read or write. Her physician noted tachycardia and an enlarged thyroid gland and referred her to the hospital.

Physical examination on admission showed a rectal temperature of 99.4°F. The respirations were 30, the heart rate 106 per minute and the blood pressure 220/120. The patient was a thin, hyperactive, chronically ill, aphasic woman. She exhibited dyspnea and orthopnea. The eyes were prominent and showed lid-lag. Arteriovenous nicking was visible in the fundi. There was slight right-facial weakness, and the tongue deviated to the right. The neck veins were distended. The thyroid gland was soft and symmetrically enlarged to 2 or 3 times the normal size, but no bruit was audible. Examination of the lungs was normal except for some moist rales at the left base. The heart was slightly enlarged to the left. A gallop rhythm and a rough systolic murmur were heard at the apex and base. The outstretched hands showed fine tremor. The dorsalis-pedis pulses were of good quality. Peripheral and sacral edema were absent. Reflexes were normal.

Laboratory examinations showed a urinary specific gravity of 1.020 with a green test for sugar and + albumin; the sediment contained 15 to 20 leukocytes, 0 to 2 erythrocytes and 0 to 2 coarse granular casts per high-power field. The blood hemoglobin and leukocyte counts were normal. The blood sugar was 178 mg. per 100 cc. 1 hour after ingestion of glucose and 124 mg. per 100 cc. 2½ hours afterwards. The blood nonprotein nitrogen concentration was 25 mg. per 100 cc. The basal metabolic rate measurements were +1 and +21. Tracer study with radioiodine (I^{131}) revealed 93.5 per cent excretion in 24 hours. The electrocardiogram showed left-axis deviation. Findings on lumbar puncture were normal. Roentgenogram of the chest showed the heart to be slightly enlarged.

There was slow progression of the neurologic symptoms and signs; responsiveness decreased, and a complete right hemiplegia was present at the end of a week.

On the 11th hospital day the patient was given intravenously 26 mg. of SKF No. 501 (0.5 mg. per kg.) dissolved in 10 cc. of distilled water. She was not receiving barbiturates. The blood pressure, which had previously ranged from 190/110 to 250/150, fell to normal within 1 hour and remained at that level for twenty-four hours, after which there was a gradual return to pre-injection level (Fig. 1). This response is very similar to that described in the patient with pheochromocytoma of Koffler and others,[16] referred to above.

Evidence of the completeness of adrenergic blockade during the hypotensive period was obtained from the response to epinephrine (Fig. 2). Subcutaneous injection of 0.2 mg. of epinephrine (adrenalin) given five hours after the administration of SKF No. 501 caused a fall in blood pressure from 128/68 to 92/46, with a rise in heart rate from 132 to 148; 0.1 mg. of epinephrine injected subcutaneously twenty-three hours after administration of the adrenolytic agent caused a fall in blood pressure from 160/84 to 108/60, with a heart-rate increase of 136 to 148. This is the reversal phenomenon described in animals who have received injections of epinephrine after adrenergic blockade with dibenamine,[14] and in 1 patient by Hecht and Anderson.[15]

After the appearance of the hemiplegia, fever appeared, despite the administration of penicillin. Deterioration was steady, and the patient died on the nineteenth day. At post-mortem examination, despite a careful search, no tumor of chromaffin tissue could be found. The thyroid gland showed chronic thyroiditis, and the usual evidences of advanced hypertensive disease were present.

Conclusions

An "adrenolytic" agent (N-9-fluorenyl, N-ethyl-β-chloroethylamine), a dibenamine congener, produced adrenergic blockade, as evidenced by epinephrine reversal, and lowered the blood pressure to normal for one day in a patient with sustained hypertension. At post-mortem examination no chromaffin tumor could be found.

In view of the high incidence of hypotensive responses to dibenamine in hypertension, it is unlikely that such responses can be considered in any degree as specific as the response to benzodioxane.

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References

1. Roth, G. M., and Kvale, W. F. Pharmacologic tests as aid in diagnosis of pheochromocytoma. *Mod. Concepts Cardiovas. Dis.* **18**:41, 1949.
2. Taliaferro, I., Adams, R. A., and Haag, H. B. Benzodioxan test: fall in blood pressure following its use in case of renal hypertension. *J. A. M. A.* **140**:1271-1273, 1949.
3. Rochlin, I. Personal communication.
4. Goldenberg, M., Snyder, C. H., and Aranow, H., Jr. New test for hypertension due to circulating epinephrine. *J. A. M. A.* **135**: 971-976, 1947.
5. Grimson, K. S., Longino, F. H., Kernodle, C. E., and O'Rear, H. B. Treatment of patient with pheochromocytoma: use of adrenolytic drug before and during operation. *J. A. M. A.* **140**:1273, 1949.
6. Drill, V. A. Reactions from use of benzodioxane (933F) in diagnosis of pheochromocytoma. *New Eng. J. Med.* **241**:777, 1949.
7. Green, D. M., and Peterson, E. M. Hypertensive encephalopathy after administration of benzodioxan. *J. A. M. A.* **142**:408, 1950.
8. Barnett, A. J., Blacket, R. B., Depoorter, A. E., Sanderson, P. H., and Wilson, G. M. Action of noradrenaline in man and its relation to pheochromocytoma and hypertension. *Clin. Sc.* **9**:151-179, 1950.
9. Spear, H. C., and Griswald, D. Use of dibenamine in pheochromocytoma: report of case. *New Eng. J. Med.* **239**:736-739, 1948.
10. Koffler, I., Buck, G., Wingard, C., Hitchcock, P., Guthrie, R., and Teague, R. S. Case of pheochromocytoma: diagnosis by benzodioxane test, urinary hormone studies, and nor-epinephrine assay of tumor. *J. Clin. Endocrinol.* **10**:897-903, 1950.
11. Shapiro, A. P., Baker, H. M., Hoffman M. S., and Ferris, E. B. Pharmacologic and physiologic studies of case of pheochromocytoma. *Am. J. Med.* **10**:115-130, 1951.
12. Haimovici, H., and Medinets, H. E. Effects of dibenamine on blood pressure in normotensive and hypertensive subjects. *Proc. Soc. Exper. Biol. & Med.* **67**:163-166, 1948.
13. Hecht, H. H., and Anderson, R. B. Influence of dibenamine (N-N-dibenzyl-β-chloroethylamine) on certain functions of sympathetic nervous system in man. *Am. J. Med.* **3**:3-17, 1947.
14. Wunsch, R. E., Warnke, R. D., and Myers, G. B. Effects of dibenamine on severe hypertension. *Ann. Int. Med.* **33**:613-628, 1950.
15. Nickerson, M., and Goodman, L. S. Pharmacological properties of new adrenergic blocking agent, N,N-dibenzyl-β-chloroethylamine (dibenamine). *J. Pharmacol. & Exper. Therap.* **89**:167-185, 1947.
16. Fellows, E. J. Personal communication.

MEDICAL PROGRESS

PLASTIC SURGERY: HARELIP AND CLEFT PALATE*

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With a Section on Speech Therapy by

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IT IS estimated that congenital clefts of the face occur once in 900 live births. This is the generally accepted factor in an area with a predominantly white population. Davis,[1] in Baltimore, reported an incidence in the Negro population half as great as that in the white race (1:1788). In Wisconsin,[2] where all congenital anomalies are recorded within thirty days after birth, the reported incidence is 1 in 770 births.¶ On the basis of these figures, it is calculated that approximately 270 babies with harelip or cleft palate or both are born annually in the six New England states. The purpose of this review is to call attention to the problems that these babies present to the parents, the plastic surgeon, the pediatrician, the speech therapist, the orthodontist, the prosthodontist and the social agencies, — any or all of whom may be concerned in the patient's rehabilitation.

The most recent report on this subject to appear in the *Journal* was written in 1926 by Ladd,[3] who reported his experiences with harelip and cleft palate. During the quarter-century since that report, an even broader understanding of the numerous and varied problems in the care of these patients has evolved. Collaboration today between persons skilled in treating them has afforded far greater hope to the parents and to the patient of securing a satisfactory final result.

It was over one hundred years ago (1843) that J. Mason Warren,[4] one of the first surgeons in New England interested in plastic surgery, described a method of simultaneous closure of congenital clefts of the hard and soft palate. By the use of mucoperiosteal flaps from the borders of the cleft hard palate, Warren was able to complete the closure of the palate in a single operation. He reported 14 cases. Prior to 1826 it had been customary to close the soft palate only. In that year Dieffenbach[5] showed that operative closure of the hard palate as well as the soft palate was possible. His

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¶Massachusetts State law now requires the reporting by the physician of all visible congenital anomalies within sixty days after birth. These reports are submitted to the town or city clerk, who forwards them to the State Department of Public Health in Boston. This report is not open to public inspection but is used by the department in connection with its program for Crippled Children. A fee of 50 cents is paid by the State for each report, 25 cents of which is paid to the physician who submits the report.

was a two-stage rather than a one-stage procedure. Today the names of these pioneers in the surgery of cleft palate have been linked, for the palate operation is often described as the Dieffenbach–Warren procedure.[6]

Embryology

The "classical" concept of the normal embryology of the face is generally taught in the United States. According to it, five major processes or projections develop about the rim of the invaginated primitive oral cavity; these grow forward and fuse to form the normal face. Superiorly there is the frontonasal process, which is subdivided into four minor processes. Laterally there are the two maxillary processes and inferiorly there are the two mandibular processes. Failure of fusion between any part of two or more of these processes results in a facial cleft. For example, failure of the frontonasal process to fuse with one of the maxillary processes will result in a cleft of the lip or palate on that side.

Doubt about the theory of "fusion" arose as a result of studies published by Pohlmann in 1910.[7] He examined a series of cat embryos, using all available technical and optical aids, and concluded that the processes about the primitive oral cavity do not exist. Faulty interpretation of the microscopical findings in the embryo is thought to have led to the erroneous conclusion. According to Pohlmann and Veau,[8] a thickening of the ectoderm arises along the upper margin of the invaginated oral cavity and then invaginates on either side of the midline to form the primitive nostrils. An ectodermal "hood" develops over the front of the

Figure 1. *Section through Embryonic Palate, Showing Unequal Penetration by Mesodermal Tissue. An unsupported ectodermal membrane remains on the left.* (*After Veau.*)

oral cavity adjacent to the primitive nostrils. These ectodermal tissues are invaded by mesoderm from the edges of the oral cavity, forming the upper lip, alveolus, teeth, muscles and so forth.

Pohlmann believes that the development of clefts of the lip, alveolar process or anterior palate are the result of incomplete or absent penetration of the ectodermal wall by mesodermal tissues (Fig. 1). With no mesodermal supporting structure, the ectodermal membrane ruptures and a complete cleft is formed. If there is minimal penetration a narrow band of tissue may bridge the cleft (Fig. 2). The not infrequent presence of such bands across the cleft is considered significant evidence of such a partial penetration of the ectoderm by the mesodermal tissue with a rupture of the ectodermal membrane in the remainder of the lip.

Figure 2. *Narrow Bridge Across an Otherwise Complete Cleft of the Lip and Palate.* (*After Veau.*)

The extent of mesodermal nonpenetration thus determines the severity of the cleft.

Only in embryologic closure of the posterior palate is there fusion of processes from either side. These processes arise from the lateral walls of the nasal and oral cavity to form the posterior palate. A cleft of the posterior palate alone, therefore, results from failure of fusion of the two embryonic palatal processes. It is always a midline cleft, thus differing from clefts of the lip and alveolus.

Whether the cleft lip causes an associated cleft of the palate or whether the latter is independent of it is still undetermined. The frequent simultaneous recurrence of the two suggests a common etiology. However, the fact that the alveolus and the lip are formed earlier than the posterior palate suggests that the cleft lip is a precursor of the cleft palate but makes it seem doubtful that the cleft posterior palate influences the development of a cleft lip or alveolus.

The implication of a maldeveloped mesoderm in the formation of clefts of the face is a very attractive concept. Clinically it has been observed that these patients often have difficulty in speech despite excellent anatomic and functional restorations of the lip and palate. Certain sounds, for example, the "S" sound, which is not formed in the nasopharynx, may be difficult for the patient with a repaired cleft palate to execute. Such deficiencies have been hard to explain but may be the result of more diffuse imperfections of adjacent mesodermal structures than are apparent with our present method of examination. These will be discussed more fully in the section on speech therapy.

Etiology

The causes of harelip and cleft palate are not known. It is generally agreed that heredity is an important factor. W. B. Davis, in 1928,[9] reported

a family history of either cleft lip or cleft palate or absence of one or both upper lateral incisor teeth in the past three generations in 57 per cent of patients. Sanders[10] analyzed statistically the histories of all children operated on for congenital cleft from 1912 to 1933 in the Rotterdam municipal hospitals. He found that:

> 44.5 per cent of the cases studied had a positive family history.
>
> One out of 16 persons in Holland carried a hereditary disposition. This figure may appear high, but the national incidence of the congenital clefts is only 1:954.
>
> The hereditary disposition is a recessive characteristic, less recessive in the female than in the male.
>
> An incidence of 1:100 was discovered in one Dutch town in which investigation of ancestral patterns showed a considerable degree of inbreeding. Some parents were found to be related through as many as six different lines.

Fogh-Andersen[11] in 1942 wrote a very exhaustive treatise on "Inheritance of Harelip and Cleft Palate." He studied over 700 patients in Denmark with clefts of the lip or palate. He differentiates two malformations without genetic connection. These are: harelip with or without cleft palate and isolated cleft palate. The former occurs most frequently in males (68.37 per cent), particularly in the severest forms, and the latter more frequently in females (66.1 per cent). A family disposition of 27 per cent in harelip alone and 41 per cent in harelip with cleft palate but only 19 per cent in isolated cleft palate was demonstrated. Geographical and social factors, age of parents, conditions of pregnancy and delivery could not be shown to influence significantly the occurrence of facial clefts. Analysis of his figures has shown that harelip with or without cleft palate must be considered hereditary, whereas other factors are significant in isolated cleft palate.

In this country very similar figures of incidence have been gathered. Davis[1] reports an incidence of harelip in the male of approximately 70 per cent compared to 30 per cent in the female. Cleft palate, on the other hand, is reported by Davis and Vaughan[12] to be 55 per cent in the female and 45 per cent in the male.

A number of interesting statistical observations bearing on congenital malformations have been made by Murphy,[13] who analyzed the records of the Pennsylvania Bureau of Vital Statistics. Among the significant conclusions he found that older mothers (forty years and older) have malformed children 3 times as frequently as those between fifteen and thirty years of age. Furthermore, families with a congenitally malformed child proved 24 times as likely to have other deformed children as is the population at large. Finally, periods of nonchildbearing averaging five years or more not infrequently produced the birth of a deformed child. He cites the interesting family history of a father who had a child with cleft lip and palate by each of two wives.

A recent statistical study by Stevenson, Worcester and Rice[14] at the Boston Lying-in Hospital does not confirm Murphy's conclusions that older mothers are more prone to have deformed children. According to the figures of the Boston Lying-in Hospital, the deformed child of an older mother is less likely to survive, and consequently a study based on an analysis of death certificates may lead to erroneous conclusions. Stevenson reports that the incidence of anomalies was high during 1935 and reached a peak seven months after a widespread epidemic of rubella. Another interesting observation is the high incidence of anomalies among infants conceived during the fourth and first quarters of the year, when respiratory diseases are common. Finally, anemia, febrile illness and chronic illness were not uncommon in mothers of these deformed children.

On the other hand, the experimental production of cleft palate in rats by a maternal nutritional deficiency (riboflavin) has led Warkany[15] to wonder if less significance should be attached to the genetic factor in etiology. He points out that a high family incidence may indicate merely that the whole family is affected by unfavorable environmental influences. In addition, he recalls that rickets was thought to be greatly influenced by heredity fifty years ago. One may conclude from his observations that maternal well-being is important to the normal development of the embryo.

Warkany noted micrognathia associated with cleft palate in some of the animals. This syndrome has been reported in the human being and has presented problems of survival because of obstruction of the airway by the unsupported tongue. By producing a temporary surgical adhesion between the tongue and the lower lip, Douglas[16] has been able to control the tongue and simplify postnatal care.

Another factor in "isolated cleft palate" was reported in 1950 by Ingalls.[17] He was able to produce a cleft palate experimentally in the mouse fetus by subjecting the mother to five hours of anoxia on the fourteenth day of gestation.

The lower incidence of clefts of the face in the Negro,[1] which is one half as great as in the white race, remains unexplained. Likewise unexplained is the occurrence of harelip more than twice as frequently on the left side as on the right. Clefts of the lip and palate on the right side are actually less frequent than are double clefts of the lip associated with a palate cleft.

Other factors that may influence the development of harelip and cleft palate have been reviewed by Kiskadden.[18] He points out the significance of "organizers" or "inducers." These chemical substances, which act on embryonic cells, alter their pattern of growth. For example, the development of the optic cup from the neural plate is induced by a portion of the archenteric roof immediately beneath it. Transplantation of this tissue beneath the epidermis elsewhere will produce eyes in this abnormal location. The timing of such transplantation is important because the process continues step by step with each stage, acting as the inductor of the next. Any interruption of the progression of development produces an abnormality. Only a limited number of organs have been studied, but as evidence accumulates a better understanding of the factors producing congenital clefts of the face may be found.

Other possible predisposing causes of congenital deformities for which there is some evidence are: nutritional and vitamin deficiencies in the mother — clefts are said to occur more frequently in poorer families than among the well-to-do; hormonal influences — Baxter[19] has recently reported a 44 per cent incidence of cleft palate in the offspring of female mice treated with cortisone; virus disease — rubella, for example, is known to be a factor in congenital cataract, heart defects, deafness and dental abnormalities.

Anatomy of the Palate

Significant features of the anatomy of the palate have been carefully described by Dorrance[20] and Oldfield.[21] The hard palate is an immovable structure that, unless it is the site of a perforation, does not influence the formation of sounds. The soft palate is divided into three parts. Anteriorly it is a thin membrane acted on by the tensor palati muscle to make it a firm diaphragm. The middle segment of the soft palate is easily movable and is traversed by the levator muscle, which moves it upward and backward against the posterior and superior walls of the nasopharynx to occlude the opening. The posterior segment is a loose apron that moves only with the middle segment.

The levator palati muscle arises from the petrous portion of the temporal bone and passes adjacent to the superior pharyngeal constrictor, which pulls at a right angle to the levator, forming a circular ring of muscle. The superior constrictor muscle envelops the posterior and lateral walls of the upper pharynx. Contraction of the levator forms a ridge on the upper surface of the palate, which makes contact with the so-called Passavant cushion on the posterior pharyngeal wall. Passavant (1863)[22] described this cushion as formed by special transverse fibers of the superior constrictor. According to Wardill,[23] it remains erect during speech.

The tensor palati muscle arises high on the inner surface of the pterygoid plate, passes downward and forward, forming a tendinous band that hooks around the hamular process to turn medially at a right angle, and inserts at the anterior segment of the palate. The tensing of the palate is considered an important part of swallowing in providing a firm surface against which the tongue can act. In operations for cleft palate the hamular process is fractured. This reduces tension on the suture line in the thinnest and weakest part of the palate, where perforation is most apt to occur. Fracture of the hamular process converts the tensor into a levator that re-enforces the action of the levator muscle.

Time for Operation

The operation for cleft lip should be done in the first few months of life. It may be done within the first twenty-four hours of life if the baby is healthy in every other respect. Operation at this time has certain social and economic advantages. The mother need never see the deformed baby. Another period of hospitalization for the baby will be unnecessary. The problem of feeding will be simplified, and the baby may be discharged from the hospital with the mother or shortly after the mother's discharge. With proper anesthesia and adequate supportive treatment, the operation offers no greater risk than one done several weeks later. Normal feeding can be begun on the second or third day.

If early operation is impossible, closure of the lip should be postponed at least until after the birth weight has been regained, — usually in two or four weeks.

There is a great difference of opinion about the proper time for operation on the palate. On the one hand is the desirability of closing the palate before speech habits are established. On the other hand, recent investigations[24, 25] have shown that surgical procedures performed early may be followed in some cases by underdevelopment of the face, — the result of either scarring or interference with the blood supply to the growing bone.

For best results in speech, operation before the age of eighteen to twenty-four months is desirable. Operation performed earlier than eighteen months carries certain unwarranted risks. However, multiple procedures at this age, necessitated by failure of the first attempt at closure, may produce deforming scars, interference with mobility of the palate and interference with normal bony growth. Such a catastrophe should be avoided.

The evidence for delaying palate repair is based on studies of facial development in which a cephalometer was used.[24] Approximately five-sixths of the total breadth of the palate is present at four years, and the complete breadth is present at ten years. Graber has found that surgical operation may limit

the growth of the maxillas by comparison with the normal vertical and lateral growth in unoperated patients. However, it must be pointed out that the greater the number of operations necessary for completing the repair, the greater has been the abnormality of growth.

The logical conclusion to be drawn is that early operation (at 18 to 24 months) is desirable but closure of the palate must be completed in a single procedure. Failure to accomplish this is in most cases evidence of technical errors in performing the operation.

Operative Procedures in Unilateral Harelip

The aim of the harelip repair is twofold: to produce a normal full infant lip and to correct the often extreme deformity of the nose. The details of various methods whereby these aims may be accomplished are found throughout the literature of plastic surgery.[26] Either of two methods may be used in these repairs. The older of these is the V-excision in which the edges of the cleft are cut open in straight or curved lines and united. Certain disadvantages are noted in this type of repair. The straight vertical scar of closure shortens and pulls the vermilion border upward. There is a tightness of the lip at the lower border where it is normally full, and a deficiency of mucosa medial to the line of closure may produce a notching of the lip.

In the second method a flap is utilized. This may be rectangular, square, triangular or from either columellar or cleft side or may take the form of multiple flaps. The principle of using a flap has been generally credited to Mirault (1844). Blair and Brown[27] called attention to the method in 1930, and Brown and McDowell[28] described a variation of it in 1945 (Fig. 3). It has been the one most generally used in this country since 1930. The use of a flap has the advantages of utilizing the thicker vermilion from the cleft side to increase the fullness of the vermilion tissue in the center of the lip.

In carrying out the procedure it is customary to mark the incisions accurately and plan the procedure before any cuts are made. Complete mobilization of the lip is impossible without relaxation of the cheeks by wide undermining to free all attachments to the bony structures of the face. This undermining may have to extend laterally to the malar bone and superiorly to the orbital border. Both cheeks must be loosened, not only to permit relaxed closure of the lip but also to allow the columella to be brought to the midline and the deformed ala to be rotated against the base of the columella. To avoid wrinkling of the lining of the ala as it is turned medially, the overlying skin is freed from the alar cartilage, permitting the two surfaces to adjust to each other.

Closure of the alveolar cleft at the time of the lip repair by a wire suture through the maxillas has been advocated by some writers.[29] The procedure has been generally discarded because of risks to the tooth buds in and above the alveolus, because of possible damage to the bone and finally because the muscles of the repaired lip have proved a most effective force in closing the bony cleft. Within a matter of months after the lip is closed most alveolar processes will be in contact and the width of the palate cleft reduced.

Closure of the anterior palate is occasionally carried out in conjunction with the lip repair.[30] A mucoperiosteal flap is shifted from the cleft side and attached either to a vomer flap from the opposite side or to the corresponding mucoperiosteal flap on the uncleft side. It is claimed that this makes the posterior palate repair easier and provides a good nasal floor. The early closure of the anterior palate is by no means a universal practice, as complete closure of the front of the palate after the alveolar separation is reduced can be accomplished in conjunction with the repair of the rest of the palate. Or it may be done as a preliminary step to final closure or elongation of the soft palate.[30]

Figure 3. *Method of Unilateral Harelip Repair (after Brown and McDowell).*

Operative Procedures in Bilateral Harelip

The double harelip presents multiple special problems not found in the single harelip. The repair is "about twice as difficult as in single clefts and the results are about half as good."[31] The difficulties are centered in the prolabium and premaxilla, which in most cases are completely detached from the lateral segments of the upper lip and the two alveolar processes. The premaxilla often projects forward beyond what seems to be the normal prominence of the lip, and the columella is usually correspondingly short. At birth the supporting cartilage behind the premaxilla may be deviated into one or both nasal airways. If deviation is not already present it may develop later because of backward pressure of the closed lip. In order to minimize the tension on the suture line at the time of closure and to avoid future buckling of the septum, a rectangular segment of vomer is sometimes removed at the primary repair and the premaxilla is displaced backward. It is undesirable to disturb the position of the premaxilla, as abnormal

reduction of the prominence of the lip may result. Whether the retraction of the lip is solely a consequence of removing the bone or whether there is interference with growth of the vomer as well is still undetermined. In any case, the vomer should not be disturbed unless it is absolutely necessary.

The increasing interest in the effects of operation on the blood supply to the growing facial bones and the desirability of leaving the vomer undisturbed have stimulated the undertaking of the repair as a two-stage procedure,[32] closing one side at a time with an interval of several weeks between operations. Those who advocate this method report that section of the vomer is not necessary and that closure with little tension and minimal risk of separation at the suture line is possible. Not infrequently repair of the lip is combined with closure of the anterior palate, as is occasionally done in repair of the unilateral harelip.

The standard procedure (Fig. 4) in double-harelip repair consists in the outlining of incisions along the border of each lateral segment of the lip to correspond to similar incisions on the prolabium. A flap similar to that described in single harelip repairs is marked out on each lip. The width chosen for these flaps is determined by the size of the

FIGURE 4. *Method of Bilateral Harelip Repair (after Brown, McDowell and Byars).*

prolabium. Asymmetrical flaps may be necessary if the two sides of the cleft are of different shape. When the incisions are made all membrane from both lips and prolabium must be preserved in order to leave enough for closure in the midline below the prolabium and to provide lining on the undersurface of the two halves of the lip. Wide undermining of the cheeks to mobilize and reduce tension on the lip, the separation of the alar cartilage from the overlying skin and the closure of the lip are similar to the procedures carried out in unilateral harelip. Multiple flaps of membrane are then fitted and notching is avoided. If a partial cleft is present on one or both sides, it may be difficult to find sufficient membrane to avoid a notch. Excessive sacrifice of skin to secure sufficient membrane will exaggerate the vertical length of the upper lip and create a deformity that is difficult to correct.

Most patients, even with the most expert primary repair of the lip, will need correction of secondary deformities. The short columella is the commonest of these. At the age of four or five years the so-called trefoil operation[31] is carried out. A three-pronged flap of skin from the prolabium is shifted forward to increase the length of the columella. If a deficiency of skin in the lip results from this procedure or if there is a pre-existing deficiency of membrane or skin, a split vermilion-bordered flap may be used to correct the deformity.[33] At opera-

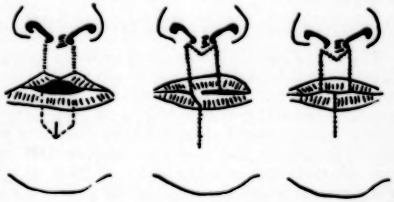


FIGURE 5. *The Split Vermilion-Bordered Lip Flap in Secondary Bilateral Harelip Repairs.*

tion the remainder of the prolabium is intentionally sacrificed and a flap from the lower lip shifted into the upper to replace it (Fig. 5). The flap provides abundant tissue for the upper lip and sufficient mucosa for deepening the upper buccal fornix, and at the same time reduces the abnormal fullness of the lower lip.

The fixation of the premaxilla is still an unsolved problem.[31] It is important, as teeth located in the premaxilla will be unstable, and instability of an edentulous premaxilla makes the holding of a denture difficult. Accurate closure of the membrane at the cleft border helps to stabilize the bone, but thus far no method for the creation of a firm bony union has been devised. The mobility in some patients with a small edentulous premaxilla is so great that elective excision of the bone has been done and a denture used to maintain the fullness of the upper lip. This procedure has little to recommend it, however.

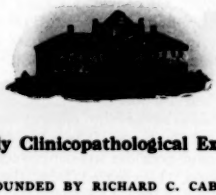
(To be concluded)

REFERENCES

1. Davis, J. S. Incidence of congenital clefts of lip and palate. *Ann. Surg.* **80**:363-374, 1924.
2. Phair, G. M. Wisconsin cleft palate program. *J. Speech Disorders* **12**: 410-414, 1947.
3. Ladd, W. E. Harelip and cleft palate. *Boston M. & S. J.* **194**:1016-1025, 1926.
4. Warren, J. M. Operations for fissures of soft and hard palate. *New Eng. Quart. J. Med. & Surg.* **1**:538, 1843.
5. Dieffenbach, J. F. Über das Gaumensegel des Menschen und der Saeugethiere. *Litt. Ann. d. ges. Heilk.* **4**:298, 1826.
6. Blair, V. P., and Brown, J. B. Dieffenbach-Warren operation for closure of congenitally cleft palate. *Surg., Gynec. & Obst.* **59**:309-320, 1934.
7. Pohlmann, E. H. *Die embryonale Metamorphose der Physiognomie und der Mundhohle des Katzenhopfes.* Dissertation. 62 pp. Leipzig, 1910.

8. Veau, V. Hasenscharten menschlicher Keimlinge auf der Stufe 21-23 mm. S. St. L. *Ztschr. f. Anat. u. Entwcklngsgesch.* **108**:459-493, 1938.
9. Davis, W. B. Harelip and cleft palate: study of 425 consecutive cases. *Ann. Surg.* **87**:536-554, 1928.
10. Sanders, J. Inheritance of harelip and cleft palate. *Genetica* **15**: 433-510, 1934.
11. Fogh-Andersen, P. *Inheritance of Harelip and Cleft Palate.* Copenhagen: Einar Munksgaards Forlag, 1945.
12. Vaughan, H. S. *Congenital Cleft Lip, Cleft Palate, and Associated Nasal Deformities.* 210 pp. Philadelphia: Lea and Febiger, 1940.
13. Murphy, D. P. *Congenital Malformations.* 127 pp. Philadelphia: J. B. Lippincott Company, 1947.
14. Stevenson, S. S., Worcester, J., and Rice, R. G. 667 congenitally malformed infants and associated gestational characteristics. I. General considerations. II. Parental factors. *Pediatrics* **6**:37, 208, 1950.
15. Warkany, J. Etiology of congenital malformations. *Advances Pediat.* **2**:1-63, 1947.
16. Douglas, B. Treatment of micrognathia associated with obstruction by plastic procedure. *Plast. & Reconstruct. Surg.* **1**:300-308, 1946.
17. Ingalls, T. H., Curley, F. J., and Prindle, R. A. Anoxia as cause of fetal death and congenital defect in mouse. *Am. J. Dis. Child.* **80**: 34-45, 1950.
18. Kiskadden, W. S., Schechtman, A. M., and Brock, C. Theories of etiology of congenital deformities. *Internat. Abst. Surg.* **88**:1-14, 1949.
19. Baxter, H., and Fraser, F. C. Production of congenital defects in offspring of female mice treated with cortisone: preliminary report. *McGill M. J.* **19**:245-249, 1950.
20. Dorrance, G. M., and Bransfield, J. W. Cleft palate. *Ann. Surg.* **117**:1-27, 1943.
21. Oldfield, M. C. Cleft palate and mechanism of speech. *Brit. J. Surg.* **29**:197-227, 1941.
22. Passavant, G. Über der Verschliessung des Schlundes beim Sprechen, Frankfurt 1863. Reviewed from *Schmidt's Jahrbuch* by LiMerkel of Leipzig, 350, 1867.
23. Wardill, W. E. M. Technique of operation for cleft palate. *Brit. J. Surg.* **25**:117-130, 1937.
24. Graber, T. M. Craniofacial morphology in cleft palate and cleft lip deformities. *Surg. Gynec. & Obst.* **88**:359-369, 1949.
25. Slaughter, W. B., and Brodie, A. G. Facial clefts and surgical management in view of recent research. *Plast. & Reconstruct. Surg.* **4**:311-332, 1949.
26. Padgett, E. C. *Surgical Diseases of the Mouth and Jaws.* 807 pp. Philadelphia: W. B. Saunders Company, 1938.
27. Blair, V. P., and Brown, J. B. Mirault operation for single harelip. *Surg., Gynec. & Obst.* **51**:81-98, 1930.
28. Brown, J. B., and McDowell, F. Simplified design for repair of single cleft lips. *Surg., Gynec. & Obst.* **80**:12-26, 1945.
29. Brophy, T. W. *Cleft Lip and Palate.* 340 pp. Philadelphia: P. Blakiston's Son & Company, 1923.
30. Waldron, C. W. Management of unilateral clefts of palate. *Plast. & Reconstruct. Surg.* **5**:322-336, 1950.
31. Brown, J. B., McDowell, F., and Byars, L. T. Double clefts of lip. *Surg., Gynec. & Obst.* **85**:20-29, 1947.
32. Huffman, W. C., and Lierle, D. M. Repair of bilateral cleft lip. *Plast. & Reconstruct. Surg.* **4**:489-501, 1949.
33. Cannon, B. Split vermilion bordered lip flap. *Surg., Gynec. & Obst.* **73**:95-97, 1941.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 37311

PRESENTATION OF CASE

A sixty-three-year-old man entered the hospital complaining of left-flank pain.

For several years the patient suffered from angina pectoris and exertional dyspnea for which his physician prescribed nitroglycerin and digitalis. He had frequent upper-respiratory infections for six months prior to entry. Two months before admission he was hospitalized for "virus pneumonia" and treated with penicillin. He recovered completely but gained back only 12 of the 29 pounds he had lost. X-ray films at this time showed cardiac enlargement, pulmonary fibrosis and emphysema. Eighteen hours prior to admission he developed sudden severe pain in the left flank radiating down to the left groin. He voided spontaneously twice soon thereafter, but passed no urine for ten hours prior to entry. A urinalysis showed microscopic hematuria. All ingested food was vomited.

Both his parents had died of "arteriosclerotic heart disease" in their seventies.

Physical examination revealed a thin, heavily sedated man vomiting and complaining of pain in the left flank. The skin was pale and cool. There was minimal clubbing of the fingers and toes. Examination of the chest revealed bronchial breathing posteriorly in the right lower lung. The heart was enlarged to the anterior axillary line; sounds were faint and of poor quality; the aortic second sound was greater than the pulmonic; no murmurs were heard. The peripheral pulses were weak. The abdomen was not remarkable. There was tenderness and a sense of fullness in the left costovertebral angle with blotchy ecchymotic discoloration of the skin over this region not extending beyond the midline.

The temperature was 98°F. orally, the pulse 70 and the respirations 24. The blood pressure was 90 systolic, 60 diastolic.

Examination of the blood revealed a hemoglobin of 14.2 gm. and a white-cell count of 33,600. Two urine specimens were amber colored, slightly cloudy and acid, had a specific gravity of 1.010 and gave a ++ test for albumin and 0 tests for sugar and bile; the sediment contained up to 75 white cells in clumps and occasional hyaline casts per high-power field but no red cells or stones. An electrocardiogram disclosed a regular ventricular rhythm at a rate of 65. The QRS interval was 0.14 sec. No P waves were made out. The Q waves were present in Leads 1, 2, AVL and AVF and large in V_4, V_5 and V_6. The R waves were absent in Leads 3 and V_2 and small in Lead V_1. The T waves were low upright in Lead 1, upright in Leads 2, 3, AVF,

V_3, V_4, V_5 and V_6, diphasic in Lead AVL, flat in Lead V_2 and inverted in Lead V_1.

Two x-ray films of the abdomen revealed extensive calcification in the aorta. There were two somewhat rounded calcifications overlying the left sacrum. The kidneys were not grossly remarkable. The heart shadow seen on the abdominal films appeared enlarged. There was a definite suggestion of disease probably of long standing in the left lower lobe and to a lesser extent possibly in the right lower lobe.

On the day after entry the patient was noted to be clammy and pale. He complained of intermittent attacks of severe epigastric cramps and pain in the left shoulder requiring morphine. The pulse was barely perceptible. The apical rate was regular at 60 beats per minute, the heart sounds distant and of only fair quality. A Grade I apical systolic murmur was heard for the first time. There was exquisite tenderness in the left costovertebral angle despite administration of opiates. Peristalsis was fairly normal. Because of his general condition and a blood pressure of 72 systolic, 50 diastolic, he was put on shock blocks, with slight general improvement. A transfusion, however, was believed necessary. While this was being administered his right arm suddenly shot up in the air and he became rigid and died, fifty hours after admission.

Differential Diagnosis

Dr. Jacob Lerman*: Certainly the history of respiratory infections and the x-ray changes in the lung fields point to some disease in the lung. He had an acute onset of left-flank pain radiating to the groin, followed by microscopic hematuria. Clinically a renal calculus would be the most common lesion one would expect with this sort of story. It is hard for me to visualize anyone's dying from a renal calculus in a couple of days; if he had complications such as pyelonephritis or renal shutdown it would take a couple of weeks. The clubbing of the fingers points to a pulmonary lesion, the nature of which might be discovered from the x-ray films.

On physical examination he had a large heart. The aortic second sound was greater than the pulmonic, which suggests that he had hypertensive heart disease in the past, even though the blood pressure was low on admission. The electrocardiogram indicated chronic coronary-artery disease with bundle-branch block. The ecchymotic discoloration in the left costovertebral angle suggests three possibilities: a perinephric abscess, hemorrhage around the kidney or thrombosis of the renal vessels.

I think I had better see the x-ray films now. I may get some help from them.

Dr. Joseph Hanelin: We have films of the chest made in another hospital six weeks before admission here. A portable chest film shows mottled density in both lungs compatible with widespread infection. The right costophrenic sulcus is blunted, and the heart is somewhat enlarged. Conventional chest films made several weeks later show clearing of the pneumonic process. There is evidence of considerable pulmonary emphysema. Persistent blunting of the right costophrenic sulcus appears to result from pleural thickening. There is rather peculiar calcification in several scattered zones, principally in the right lung, somewhat resembling the pattern of retained lipiodol. In addition to emphysema, there is pulmonary fibrosis and probable basal bronchiectasis. A film of the abdomen made on admission shows calcification within the upper-abdominal aorta, indicating only slight increase in caliber. The two small calcifications described in the protocol overlying the left sacrum could well represent vascular calcification rather than ureteral stones. Kidney outlines appear normal; the left kidney may be slightly larger than the right. I can make out no abnormal abdominal mass.

Dr. Lerman: There was mentioned a pulmonary lesion seen in the abdominal films.

Dr. Hanelin: The streaky densities described in the lower lung fields may in part represent calcifications.

Dr. Lerman: Of course, I should like to relate the pulmonary findings, obtained both clinically and by x-ray examination, to the pain in the flank. I know the patient had coronary heart disease and probably hypertensive heart disease. I am somewhat disturbed by the x-ray appearance of the heart as compared to the clinical impression of enlargement of the heart. The types of pulmonary disease I should consider are emphysema and pulmonary fibrosis. I expected from the description and the finding of bronchial breathing that he also had chronic bronchiectasis. There certainly is little to suggest tumor of the lung.

Is it possible to explain all the symptoms, including the terminal episode, by disease in either the lungs or the heart? The heart seems to be a logical place to look for trouble. He undoubtedly had long-standing heart disease and could easily have developed acute coronary thrombosis, which often leads to mural thrombi, with resultant embolus and infarction of the kidney. Certainly infarction of the kidney is associated with pain that might radiate to the groin, although this is rather dubious; I have never seen pain radiating to the groin in such a situation. The urinary findings, — slight hematuria and later on cells and casts, — are consistent with that sort of supposition. Coronary thrombosis would explain the severe pain in the epigastrium and pain radiating to the shoulder. The final episode, the convulsive motion of the right arm with rigidity, might also be explained by embolus to the brain. A diagnosis of coronary thrombosis with complications resulting from it would explain everything.

*Associate physician, Massachusetts General Hospital.

What other vascular conditions should be considered? A man who had respiratory infections for several months could develop an endocarditis. It seems unlikely; there was no evidence of a septic process going on for several months. However the embolic phenomena, — emboli to the kidney and brain, — and also the development of the murmur could be blamed on an endocarditis. I am not impressed by this possibility, because there was not much evidence of peripheral emboli, sepsis and so forth.

It is possible that the emboli were septic in nature, coming perhaps from a lesion in the lung — bronchiectasis or some bronchial infection, as indicated by x-ray examination. I suppose a perinephric abscess could come from the lung. Terminally, a brain abscess could come from the lung also, but usually such episodes are associated with a very severe type of pulmonary suppuration in which there is severe cough, fever, sputum, hemoptysis and so forth. This, too, I think is very unlikely.

The high degree of arteriosclerosis raises the possibility of a dissecting aneurysm. This would not explain very much more than pain in the epigastrium and pain in the shoulder. It is hard for me to visualize a dissecting aneurysm producing pain in the flank as an initial symptom. Consequently I shall discard it.

I was hoping I could explain some of the renal findings by amyloidosis, in relating them to the pulmonary lesion, but there certainly is not enough pulmonary infection to suggest amyloid disease. Could pain in the flank or groin be due to involvement of the kidneys by polyarteritis? Again, I cannot find enough evidence to tie in polyarteritis, although it is possible. I am left with a major diagnosis of coronary-artery disease, with coronary occlusion and mural thrombus, with embolic phenomena to the kidneys and brain.

A Physician: How would you explain the ecchymosis around the left kidney?

Dr. Lerman: I suppose if there is infarction there may have been some hemorrhage in the perirenal tissue.

A Physician: Would a hemorrhage in the retroperitoneal space answer all these questions?

Dr. Lerman: I suppose a periarteritic aneurysm might rupture there and produce hemorrhage. Then that would be the spot where one would find evidence of periarteritis. It seems a little unlikely at best.

Dr. Alexander Leaf: Could it have been aneurysm of the aorta?

Dr. Lerman: Yes, on the evidence of pain in the epigastrium and shoulder, but I do not see how dissecting aneurysm would fit in with pain in the flank. It would have to occlude the renal artery.

Dr. Leaf: Perhaps start in the region of the renal artery?

Dr. Tracy B. Mallory: In theory a dissecting aneurysm could start almost anywhere in the aorta; in fact that does not seem to be true. Almost invariably the intimal tear is found in the ascending aorta within a few centimeters of the aortic valve.

Clinical Diagnosis

?Myocardial infarction.
?Ureteral stone.

Dr. Lerman's Diagnoses

Coronary artery disease, with mural thrombi.
Emboli to left kidney and brain.
Pulmonary emphysema and fibrosis.

Anatomical Diagnoses

Arteriosclerosis of abdominal aorta, severe, with mural thrombosis.
Renal infarction, severe, with perirenal hemorrhage.
Coronary sclerosis.
Cardiac hypertrophy.
Fibrosis of myocardium.
Pulmonary emphysema, severe.
Pulmonary fibrosis, moderate.

Pathological Discussion

Dr. Mallory: The most obvious findings at autopsy were a diffusely hypertrophied heart with considerable fibrosis of the myocardium, a severe pulmonary emphysema with a moderate grade of pulmonary fibrosis, very severe atheroma and mural thrombosis of the abdominal aorta and an extensive focus of hemorrhage about the left kidney. That was partly extracapsular and partly intracapsular, and on stripping the capsule the surface of the kidney was much discolored, — a peculiar bluish purple, — suggesting hemorrhage within the parenchyma of the kidney of many hours' duration. Microscopically the kidney was extensively but very irregularly infarcted, the severity varying in degree from point to point. In some areas the infarction was complete, involving all structures of the cortex. In other areas the tubules were necrotic, but the glomeruli still seemed viable, suggesting that at least in those areas the blood supply had been diminished but not entirely cut off, so that the epithelial cells of the tubules, which are most sensitive to oxygen lack, had been affected, whereas the glomeruli and blood vessels had not as yet.

I have a picture of the abdominal aorta (Fig. 1). Although there was no clearly defined aneurysmal sac, the vessel was considerably dilated in a segment that extended from the celiac axis to just below the renal arteries. The latter are identified in the picture by the matchsticks that have been inserted in them. At first glance there seems to be a dissection of the aortic wall, but this is misleading;

there is no true dissection, which requires a splitting of the media. In this case the intima has been lifted off the inner surface of the media by old organized blood clot. The renal artery, however, was readily patent to a probe. In the aorta near its orifice were some fresher, loosely attached intimal thrombi that may perhaps have dangled over the orifice and occasionally occluded it at some phases of the cardiac cycle.

DR. LERMAN: Would you say the perirenal hemorrhage was primary or secondary to the infarction?

DR. MALLORY: Secondary. It is rather more extensive than is often seen with infarction of the kidneys, although some degree of hemorrhage,

FIGURE 1.

usually merely intracapsular hemorrhage, is quite common. Dr. Colby, have you any comment on that point?

DR. FLETCHER H. COLBY: That is a rather unusually large infarction of the kidney. Were there thrombi in the arterial branch?

DR. MALLORY: Only in the interlobular branches, — and these may well have been embolic from the aortic mural thrombi.

DR. COLBY: I think Dr. Lerman came as close as anybody could in the diagnosis.

DR. MALLORY: We have had other cases of infarction of the kidneys that have been explored in the expectation of finding a renal stone, so the clinical picture can closely simulate that of renal colic.

DR. LERMAN: Even the radiation of pain?

DR. MALLORY: Yes.

CASE 37312

PRESENTATION OF CASE

A thirty-five-year-old woman entered the hospital because of chest pain.

Two months before entry she noted dull pressing pain in the left chest, made worse by breathing and motion. Five weeks before admission she had a shaking chill. Ten days prior to entry the pain in the chest became much more severe and spread to the left upper abdomen. She developed dyspnea and orthopnea, which progressively increased, and cough productive of whitish sputum. For four days before entry she felt feverish, noted excessive thirst and was unable to sleep because of severe chest pain that made coughing and deep breathing impossible. She had noticed no jaundice or change in color of urine or stools and no abnormal blood loss.

For ten or twelve years the patient had had a high alcoholic intake and a poor diet. Thirteen years before admission, after a three-month spree, she was admitted to another hospital for two months for a "nervous breakdown," of which the only details remembered were "swollen ankles." Three years prior to entry she was studied in a second hospital because of chest pain similar to that of the illness, and a diagnosis of splenomegaly was made. An x-ray film of the chest, intravenous pyelogram, Graham test, gastrointestinal series and barium-enema examination were reported as normal.

Physical examination revealed a jaundiced, markedly dyspneic, orthopneic, obese woman complaining of pain in the left chest on breathing. There were ecchymoses over the arms and chest, a spider angioma on the chest and minimal axillary hair. The chest showed tenderness and splinting on the left with dullness to flatness and absent breath sounds below. The abdomen was markedly obese, with right-upper-quadrant tenderness. There was no edema.

The temperature was 99.4°F., the pulse 120 and the respirations 30. The blood pressure was 120 systolic, 70 diastolic.

The urine was normal except for a ++++ bile test. Three stools were clay-colored and guaiac negative. Examination of the blood revealed a

hemoglobin of 11.0 gm. and a white-cell count of 15,800. The urobilinogen was 6.24 Ehrlich units, the alkaline phosphatase 9.9 mg., the cholesterol 88 mg., the cholesterol esters 8 mg., the bilirubin 7.6 mg. direct and 10.4 mg. total, the albumin 2.76 gm., the globulin 3.34 gm. with an albumin-globulin ratio of 0.8 and the nonprotein nitrogen 24 mg. per 100 cc. The cephalin flocculation was +++ in 24 and 48 hours and the prothrombin time 29 seconds (normal, 17 seconds). The tuberculin test was negative up to 1:1000 dilution. Films of the chest and abdomen demonstrated splenomegaly and a left-pleural effusion. The liver was not enlarged.

On the second hospital day she was given Chloromycetin, 800 mg. by mouth every six hours. By thoracentesis 800 cc. of dark-brown fluid containing old blood and clots was removed. Alpha-hemolytic streptococci were cultured from the fluid and cytologic examination was negative for tumor cells. Three hundred cc. of thin, foul, brownish-red fluid was obtained on the second tap. The patient continued to have cough, fever, dyspnea and many coarse rhonchi. On the eighth day 600 cc. of dark-brown, feculent-smelling fluid was removed from the left chest. In the next few hours she developed a temperature of 104.6°F., profuse sweating and progressive confusion merging into semicoma. Crysticillin and streptomycin were started. She coughed up foul material similar to the chest fluid. On the tenth hospital day trochar thoracotomy was performed. Ten hours later the patient died.

Differential Diagnosis

Dr. Arthur S. Pier*: I tried to fit this picture to one diagnosis but finally gave up. It seems to me that there are at least two distinct entities here, the liver condition and the process in the chest. I think that the history and the clinical and laboratory findings are pretty consistent with a diagnosis of an alcoholic hepatitis with considerable parenchymal-cell damage in the liver. I suspect that the splenomegaly was on the basis of cirrhosis of the liver with resulting portal hypertension.

The lung picture is more difficult. I wonder if I may see the x-ray films, Dr. Wyman.

Dr. Stanley M. Wyman: There is a large quantity of fluid in the first film of the chest that has disappeared partially in the second (Fig. 1), presumably because of the chest tap. It is impossible to be certain of definite underlying disease in the left lung, but of course the presence of some process there cannot be excluded. The films of the abdomen show the large spleen, and the shadow of the liver is, if anything, smaller than usual. That, however, is not too reliable an observation. A barium swallow was given, and only a very small part of the esophagus is outlined, but there are no obvious varices that I can see.

Dr. Pier: No ulceration?

*Assistant in medicine, Massachusetts General Hospital.

Dr. Wyman: No evidence of ulceration. The esophagus is not appreciably displaced. The major bronchi as far as I can trace them are not remarkable, but it is impossible to exclude some disease in the left lower lobe.

Dr. Pier: There is no air under the diaphragm suggesting perforation of a viscus?

Dr. Wyman: This film was taken with the patient supine, so I could not rely on that observation. On the film taken in the upright position there is no evidence of free air beneath the right leaf of the diaphragm and, so far as I can see, none beneath the left. The stomach bubble may be separated from the shadow of the lung. That is probably due to fluid in the chest or possibly beneath the diaphragm.

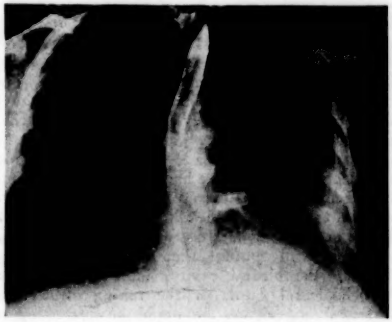

Figure 1.

Dr. Pier: Is there any pneumothorax?

Dr. Wyman: No.

Dr. Pier: In thinking this problem over I find various things running through my mind. Actinomycosis in the left chest occurred to me, but I do not think actinomycosis could give very much pleural effusion or a pleural effusion of this sort. Tuberculosis is pretty well ruled out by the negative tuberculin test, and there is nothing else that is at all suggestive of tuberculosis. When an infectious process in the lung persists in spite of treatment we always think of an underlying carcinoma. Although it is possible that she had cancer somewhere, I do not see any reason to implicate cancer in the production of these signs. We have seen cases of large pulmonary infarcts that have become infected, have broken down and have gone on to cause a hectic fever for a good many weeks, but this history is not very suggestive to me of a pulmonary infarct. How about unresolved pneumonia or a lung abscess? Certainly the fluid that was removed from the chest does not suggest the pyogenic type of abscess. It is not the sort of thing one would expect to find in

a staphylococcus abscess that ruptured into the pleural space, nor is it consistent with pneumococcus pneumonia with an empyema.

The only thing that seems to fit the picture at all is a gangrenous necrotic lesion in the lung, giving rise to the very foul chest fluid that was removed on each occasion. Pulmonary gangrene, when it is not caused by shutting off of the pulmonary artery or by trauma, is usually due to the mouth organisms, — spirochetes, vibrios and fusiform bacilli, — and results from aspiration. It usually occurs in persons with very unclean mouths and in persons who are in a weakened condition. I think the setup here would be propitious for such a development. This woman, who was an alcoholic, whose resistance was poor and who probably had bad teeth and infected gums, could have aspirated material from her mouth while she was in an alcoholic stupor. If such is actually the case, I should have expected her to have more cough earlier in the history. The history she was able to give, however, must have been quite unreliable, as evidenced by the fact that she did not even notice jaundice at the time of entry although she had a ++++ test for bile in the urine. She may have had some cough for some time before entry. I should also have expected the sputum to be quite foul if it was caused by spirochetes and other mouth organisms. Terminally she did raise foul sputum that was similar to the fluid in the pleural cavity, indicating either a bronchopleural fistula or the raising of necrotic liquefied lung tissue. It would be interesting to know if the sputum was examined under direct smear for spirochetes and fusiform bacilli. They ought to have been present, unless the gangrenous area was well walled off from the major bronchi. I should also expect the pleural fluid to show evidence of similar organisms. It did grow alpha-hemolytic streptococci that probably were swept in from the mouth and throat in the course of aspiration, and spirochetes and foreign bodies should have been present too.

Therefore, my diagnosis will rest as pulmonary gangrene involving the left lower lobe due to an aspiration bronchopneumonia. I am surprised that I do not see some evidence of a cavity or cyst in the left lower lobe, but the x-ray films are not very clear. In addition, I think she had an alcoholic hepatitis with cirrhosis and probably splenomegaly on the basis of portal hypertension. If my diagnosis of the pulmonary condition is correct, I should like to raise the question whether penicillin helps or not in this case, — but I should think not. However, patients with pulmonary gangrene have recovered with arsenical treatment.

Clinical Diagnoses

Lung abscess.
Bronchopleural fistula.

Dr. Pier's Diagnoses

Pulmonary gangrene.
Alcoholic hepatitis with cirrhosis.
Splenomegaly.

Anatomical Diagnoses

Empyema, extensive, left chest.
Cirrhosis of the liver, alcoholic.
Bronchopneumonia.
Splenomegaly.

Pathological Discussion

Dr. Tracy B. Mallory: Dr. Pier, you were obviously disturbed, as I was, by the discrepancy between the report of foul exudate in the pleural cavity and foul sputum and the bacteriologic report of only streptococci in the material. I had one advantage over you: that I was able to check the original bacteriologic record. No spirilla or fusiform bacilli were found, but other organisms were discovered, such as *E. coli* and *B. pyocyaneus*, that would account for the foul character of the exudate. For some reason that was never copied into the hospital record.

At autopsy an extensive empyema was found in the left chest and also a patchy bronchopneumonic process in both lungs, but without any detectable abscess formation. The liver, as predicted, did show the characteristic changes associated with alcoholism and inadequate diet. It was quite large and fatty, and there were many degenerated liver cells with some acute inflammatory reaction — polymorphonuclear leukocytes. There was as yet comparatively little fibrosis, although it had begun. However, I think there was enough to explain the splenomegaly (500 gm.) on the basis of portal hypertension.

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FELLOWSHIP UNLIMITED

NEVER, probably, has there been a complete understanding by a majority of either the members or the fellows of the American Medical Association of the qualifications for and the benefits accruing to each type of adherence.

The automatic nonpaying membership that comes about as a natural consequence of acceptance in one's district and state medical societies has been vaguely understood and taken for granted; many of these members have not realized, nor do they yet understand, that to become a "fellow" of the Association some initiative must be exercised, to the extent of making application for this superior rating and paying the annual dues that go with it.

Membership in the Association, according to its handbook published in 1948, consisted of 60,276 nonpaying physicians who took a passive part in the affairs of the Association although reaping many of its benefits. The 75,424 members who paid the fellowship dues of $8.00 received the *Journal of the American Medical Association* each week and were "eligible to hold office in the Association and to participate in the work of the scientific sessions."

Such a dual classification was probably justifiable, if awkward, so long as membership was free and the revenue from the publications of the Association — including the subscription-dues of fellows — covered its expenses. Changes were on the way, however, as old *mores* gave way before new *tempora*. First the fellows, who continued to carry the ball, were penalized by an increase in fellowship dues, as it became impossible for medical journals any longer to make substantial profits for their societies.

Then came the Association's apparently necessary all-time high in expenditures (up to that time), with its costly educational campaign, entailing a voluntary assessment of $25.00 on each of its members in 1949 and the levying of annual dues of the same amount in 1950 and 1951, — to cover also the member's subscription to the *Journal of the American Medical Association*. To worse confound the general confusion, the added fiscal requirement for fellowship was retained, but at only $5.00 per annum, reducing eligibility to hold office and to participate in the affairs of the Association to a bargain rate, compared with what the noneligible members were required to pay.

A demand has consequently resulted, now that membership is providing the bulk of the revenue of the Association, to clear this confusion by eliminating what is obviously an unnecessary and may even be considered an offensive class distinction.

In recognition of this need for streamlining the national organization and adopting more democratic standards for enrollment in it, no less than three resolutions were introduced in the House of Delegates last June, each calling for a single standard of membership and the abandonment of the term "fellowship." These resolutions, which were presented by Dr. George Earl of Minnesota, Dr. George A. Woodhouse of Ohio and Dr. Leland S. McKit-

trick of Massachusetts, were referred to the reference Committee on Amendments to Constitution and By-Laws.

This committee, although approving the principle involved, hedged a bit on abandoning the term "fellowship" and recommended

> that this matter be referred to the standing committee of the House on Constitution and By-Laws, with instructions to prepare such changes in the Constitution and By-Laws, in consultation with the Board of Trustees, as may be necessary to carry out these recommendations, and with instructions to present these necessary changes to the House of Delegates at its next meeting.

It is to be expected that the House of Delegates will seize the opportunity to put the organized physicians of the nation on the same footing. Whether they are called members or fellows of the Association makes little difference, so long as they assume equal responsibilities and enjoy equal privileges within its ranks. The word "fellowship" carries certain felicitous connotations that "membership" lacks. Why should not all the members be included in that bond of fellowship, the existence of which is so essential?

TO COMFORT ALWAYS

THE letter from Dr. Francis W. Palfrey appearing elsewhere in this issue of the *Journal* will no doubt impress many of its readers, on first glance, as a simple repetition of accepted and somewhat threadbare principles of ethics. Everyone knows them, and nearly everyone practices them. What then? A more careful perusal, however, will convince the thoughtful reader that those fundamental principles cannot in fact, be overemphasized and that they are today in greater danger of being lost to sight than they have ever been before.

Dr. Palfrey has simply delivered a gentle homily on the oldest precept of humane medicine — a precept that no more suffers by repetition than does the Golden Rule or the Ten Commandments or the Lord's Prayer.

His communication repeats a simple message and an age-old warning, well known but frequently forgotten, concerning the primary function of the practitioner of medicine. It is to do good to the patient in every way possible, — and all the world at times becomes the patient, — to sympathize and comfort and console, giving of oneself in the knowledge that frequently there is little else to give and that any other gift may be tragically bare.

The letter is a reminder of the humble but cherished definition of the physician as one who may cure seldom but relieves often and comforts always; of the definition of the functions of the consultant — to make a rectal examination and console the family. And how often is the second function adequately discharged? The tenor of the letter calls to mind that grand old man of Massachusetts medicine, Dr. Alfred Worcester, who is said never to have deserted the bedside of a dying patient.

In this communication the profession of medicine has had once again brought to its attention a growing suspicion that its science is running away with its art; that its relations with the people whom it serves are not always as close or as agreeable as they should be and that the hour may be later than it seems. It is a suspicion that has come to concern most intimately a public that is fully conscious of the type of help it would like to have in its hour of need, when fear strikes deep and panic may be near at hand.

There is a new awakening — a restlessness, a searching for undeviating standards and a doubting at times of the sincerity of a profession a few of whose members seem too often to have failed in humility and in the desire to show an understanding and impart a sympathy that enrich the humblest professional offering.

STUDIES IN ATROPHIC RHINITIS

IT HAS been known for some time that histamine ionization has been of help in ameliorating the symptoms of ozena, due to atrophic rhinitis. More recently streptomycin applied locally and parenterally has been found to be effective in causing disappearance of the odor and the Klebsiella organisms in this distressing condition, although without affecting crust formation or atrophy.

Sternstein, elsewhere in this issue of the *Journal*, reports the combined use of antibiotics and vasodilators in thirteen patients with atrophic rhinitis, all of whom had chronic infection with Friedländer's

bacillus, *Escherichia coli*, *Bacillus pyocyaneus* or *Bacillus proteus*. According to his results four patients showed striking improvement, six significant improvement and three slight improvement. All seemed to benefit in some measure; no failures were recorded. The most important observation was a tendency to "reversal of the regressive changes in atrophic rhinitis with ozena."

Not all cases of so-called "halitosis" are due to atrophic rhinitis or to any other single cause, and no amount of ammoniated or any other form of dentifrice is going to improve a nasal condition or cure any underlying disease. Careful, controlled studies such as those of Sternstein are necessary if progress is to be made in the control of any pathologic condition; even "bad breath" is less offensive than the bad morals used in certain classes of radio and newspaper advertising.

"GATHER YE ROSES"

THE London *Lancet*, long recognized for its facility in garnering all the news in medicine that's fit to print, has again chalked up a double play.* This rapid passage of the ball from Kharkov Institute of Biology to *New York Times* to *Lancet* has to do with a Russian survey on longevity, which indicates that old comrades, like certain Biblical characters of whom the Soviets wouldn't even know, neither die nor fade away.

According to testimony soon to be revealed in the forthcoming book "U.S.S.R. — Country of Longevity," about to be published by the Kharkov Institute, there are currently more than 30,000 residents of the Soviet Union who are over a hundred years of age. Apparently their politics, a *sine qua non* of longevity in the U.S.S.R., must be correct, a surmise that is borne out by the case of Vassily Sergeivich Tishkin, now in his 145th year, who worked 256 days on the farm last year and trudged to the so-called polls on each election day.

Since cases prove points, Makhmud Eivazov is also mentioned, — a farmer's boy of 124 glamorous years who not only is a deputy of his local soviet but regularly bathes in a mountain stream, whether he needs a bath or not. This ritual presumably takes place in the golden summertime; in the winter there is no fishing.

*Notes and News. *Lancet* 1:1185, May 26, 1951.

A notion prevails in New York, that the mortality there, among young children, is attributable to the bad quality of the milk. No doubt it is bad stuff, owing to the unnatural aliment of the cows kept in the city.

Boston M. & S. J., *August 6, 1851*

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

INOCULATIONS AND PARALYTIC POLIOMYELITIS

Claims have recently been made that when poliomyelitis occurs within thirty days after certain immunizations the degree of paralysis is greater on the side on which the injection was made. These claims have been featured in the public press, and some parents and boards of health have been disturbed in regard to immunizations that are now needed.

The original observer in Australia was able to collect only 31 cases in which there appeared to be a relation between immunizations and increased paralysis. An observer in London was able to collect only 30 cases, and 2 other workers surveyed a large part of England and were able to find only 42 more cases. Groups of similar size have been studied in this country. As yet there are no claims that a child is more likely to die of poliomyelitis because he has had a recent immunization.

If the publicity concerning this matter is likely to cause parents to postpone indefinitely or omit immunizations of their children, we must weigh the danger of what is likely to ensue.

After many years of promoting immunizations, Massachusetts has been able to reduce deaths from diphtheria from over 500 per year to less than 25 per year and has been able to reduce deaths from whooping cough from over 400 per year to less than 15 per year. If we build up a fear of immunizations among parents in the State, we are likely to lose ground in the control of these two diseases. It would not be difficult to increase the number of deaths from them to over 100 per year by neglecting immunization programs.

It has not yet been established with certainty that increased paralysis is associated with immunizations only. Further studies are necessary to determine if similar results are not produced by other inoculations, such as drugs, hay-fever treatments, vitamins, insulin and so forth. A study of these additional factors is being made in various places, and within a year or two we should have more information on the subject.

It is generally known that poliomyelitis seldom begins to increase in Massachusetts until about the middle of August. It ordinarily reaches its peak

in September and drops to a low level by the first of November.

During the last forty-one years only 0.7 per cent of the reported cases have occurred in June and 6.3 per cent of the cases in July. In fact, nearly 80 per cent of the cases have occurred in August, September and October, most of them between August 15 and October 15.

It is generally agreed that any danger from an inoculation exists primarily during the period from one to three weeks after the injection. Anyone who is particularly concerned about inoculations, therefore, should not fear to have children immunized before the first of August or after the disease has declined to low levels.

After two years of high prevalence in Massachusetts, it is likely that there will be fewer cases of poliomyelitis this year. If so, there would be no reason to postpone any immunizations. For instance, in 1938 only 18 cases of poliomyelitis were reported in an entire year, and in 1942 the total was only 36. Certainly in those years the chances of increased paralysis after inoculation were exceedingly small. Except in years when the disease becomes highly prevalent, immunization programs during the summer and fall should be continued as usual.

The case for postponing elective throat operations during the polio season is much clearer. Those who have polio after the removal of the tonsils and adenoids usually have the worst form of the disease (bulbar), and death in this form is frequent. However, great as the danger is, postponement of the operation is recommended only in the area in which the disease is increasing or has reached a high prevalence, not in the state as a whole. We can be even more conservative in recommending the omission or postponement of immunizations, since life is not endangered, and there is only some degree of increase in paralysis on the side of the injection.

Some states have recommended the cessation of immunizations (except in some cases in infants under six months) on June 15 and until notification that poliomyelitis is at a low level in the fall. This overemphasizes the danger. It is preferable to adjust the date to the trend in the incidence of the disease, recognizing that the disease increases slowly early in the season and more rapidly later.

LABORATORIES APPROVED FOR DIAGNOSTIC SEROLOGIC TESTS FOR SYPHILIS

For convenient reference, the 36 laboratories that have been approved for diagnostic tests for syphilis to August 1, 1952, are listed below. Legally only these laboratories and the Wassermann Laboratory of the Department of Public Health may perform the *premarital* and *prenatal* blood tests required by law.

The Wassermann Laboratory, at 281 South Street, Jamaica Plain, is the only laboratory in Massachusetts whose reports for premarital purposes are recognized in other states.

Location	Laboratory
Boston	Boston Dispensary
	Boston Health Department
	Commonwealth Clinical Laboratory
	Leary Laboratory
	Massachusetts General Hospital
	Massachusetts Memorial Hospitals, Genito-Infectious Disease Clinic
Brockton	Brockton Health Department Laboratory
Brookline	Sias Laboratories
Cambridge	Mount Auburn Hospital
Clinton	Clinton Hospital
Fall River	St. Anne's Hospital
	Union Hospital
Fitchburg	Burbank Hospital
Great Barrington	Fairview Hospital
Haverhill	Hale Hospital
Holyoke	Holyoke Hospital
	Providence Hospital
Lawrence	Lawrence General Hospital
Leominster	Leominster Hospital
Lowell	Lowell General Hospital
Montague	Farren Memorial Hospital
New Bedford	Burt Laboratory
	St. Luke's Hospital
North Adams	North Adams Hospital
Norwood	Norwood Clinical Laboratory
Pittsfield	Pittsfield General Hospital
	St. Luke's Hospital
Salem	Salem Hospital
Quincy	Quincy City Hospital
Springfield	Mercy Hospital
	Springfield Hospital
Tewksbury	Tewksbury State Infirmary
Waltham	Waltham Hospital
Worcester	St. Vincent Hospital
	Worcester Health Department Laboratory
	Worcester City Hospital
	Worcester Hahnemann Hospital

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JUNE, 1951

Résumé

Disease	June 1951	June 1950	Seven-Year Median
Chancroid	4	5	1
Chicken pox	1326	1512	1665
Diphtheria	12	12	21
Dog bite	1667	1597	1432
Dysentery, bacillary	2	5	2
German measles	422	437	62
Gonorrhea	170	222	316
Granuloma inguinale	1	0	0
Lymphogranuloma venereum	0	0	1
Malaria	12	0	8
Measles	2557	4062	3011
Meningitis, meningococcal	6	4	4
Meningitis, Pfeiffer-bacillus	4	11	5
Meningitis, pneumococcal	0	8	4
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	1	1
Meningitis, undetermined	3	7	6
Mumps	1403	834	966
Poliomyelitis	7	5	2
Salmonellosis	9	3	8
Scarlet fever	292	427	427
Syphilis	176	84	243
Tuberculosis, pulmonary	200	199	199
Tuberculosis, other forms	13	20	15
Typhoid fever	1	1	2
Undulant fever	0	2	5
Whooping cough	93	500	500

Comment

The diseases notably above the seven-year median for June are German measles and mumps.

Diseases below the seven-year median for the month are chicken pox, diphtheria, measles, scarlet fever, undulant fever and whooping cough.

The number of cases of mumps is the second highest ever reported for the month of June in Massachusetts.

Only once since 1918 has scarlet fever been lower in June than the 292 cases reported here.

The twelve cases of diphtheria reported this June maintain the incidence of this disease for the second year at the lowest it has been for this month since 1944.

This is the first June since 1930 that no cases of undulant fever have been reported.

Ninety-three cases of whooping cough is the lowest incidence of the disease noted for any month in our records.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from: Billerica, 1; Boston, 6; Brookline, 1; Cambridge, 1; Gloucester, 1; New Bedford, 2; total, 12.

Dysentery, bacillary, was reported from: Belchertown, 2; total, 2.

Encephalitis, infectious, was reported from: Danvers, 1; Everett, 1; Fall River, 1; Malden, 1; Pittsfield, 1; Worcester, 1; total, 6.

Hepatitis, infectious, was reported from: Murphy Army Hospital, 2; Quincy, 1; Worcester, 1; Wrentham, 1; total, 5.

Malaria was reported from: Cambridge, 1; Murphy Army Hospital, 10; Northampton, 1; total, 12.

Meningitis, meningococcal, was reported from: Boston, 3; Haverhill, 1; Lexington, 1; Lowell, 1; total, 6.

Meningitis, Pfeiffer-bacillus, was reported from: Billerica, 1; Holyoke, 1; Malden, 1; Pittsfield, 1; total, 4.

Meningitis, mumps, was reported from: Amesbury, 1; Braintree, 1; Medford, 1; total, 3.

Meningitis, undetermined, was reported from: Clinton, 1; Fall River, 1; North Adams, 1; total, 3.

Poliomyelitis was reported from: Brookline, 1; Lee, 1; Marlboro, 2; Uxbridge, 1; Wakefield, 1; Westport, 1; total, 7.

Salmonellosis was reported from: Belchertown, 1; Braintree, 1; Brockton, 1; Brookline, 1; Everett, 1; Newton, 2; Otis, 2; total, 9.

Septic sore throat was reported from: Adams, 1; Boston, 2; Lynn, 1; Newton, 2; total, 6.

Tetanus was reported from: Abington, 1; Newton, 1; Northampton, 1; Stoughton, 1; total, 4.

Trachoma was reported from: Webster, 1; total, 1.

Trichinosis was reported from: Springfield, 1; total, 1.

Typhoid fever was reported from: Boston, 1; total, 1.

BOSTON MEDICAL LIBRARY

FOR OUTSTANDING ACHIEVEMENT

The Medical Library Association at its fiftieth annual meeting presented the Marcia C. Noyes Award for Outstanding Achievement in Medical Librarianship to James Francis Ballard, of the Boston Medical Library. Starting as a page, Mr. Ballard has served the library for nearly sixty years.

He saw the founding of the Medical Library Association in 1898 and began active participation in its affairs in 1914, when he presented a paper on "Some Problems in the Administration of a Medical Library." In 1948 he wrote the history of the first fifty years of the association.

Mr. Ballard is an authority on old and rare medical books and on the classification of medical literature. He has served on many committees of the Medical Library Association, and was its president from 1937 to 1939.

CORRESPONDENCE

FUNCTION OF THE PHYSICIAN

To the Editor: Dr. Fitz's recent article and other reports of progress have impressively brought to attention the many ways in which, in the past hundred years, medical science has given us practical measures for the control of an increasing number of diseases. Certainly, although in the remote past it was only in rare cases that a doctor could feel that he had saved a life or effected a radical improvement in the course of an illness, now such cases are common.

But must we not recognize that these scientific cures, impressive as they are, are impersonal, as in the practice of a trade?

Is there not a tendency with some busy practitioners, in seeing a new patient, to ask themselves first whether there is an opportunity for surgery or penicillin, and, if there is not, to show an attitude of frustration or disinterest?

Must we not realize that although the practitioner of a century ago had no aseptic surgery and few drugs except opium and quinine that we consider worth while, his attendance was still in constant demand and was remembered with gratitude?

Clearly there was an intangible something in his service that must not be allowed to lapse and must still be our chief reliance in the considerable proportion of patients to whom no scientific therapeutics can be applied.

An important part of the reason that these older practitioners gave satisfaction approaching that given by applied science today is the fact, which all thoughtful physicians will confirm, that in many if not most cases when a patient calls a doctor it is not because of intolerable present suffering but rather because of *fear*.

He has become conscious that something is wrong that he does not understand, and he fears that it will continue and become worse, that it may be the beginning of a prolonged illness, — perhaps even disabling or fatal. This fear, moreover, is commonly combined with a peculiarly oversensitive emotional state. So he consults a doctor as one who, he hopes, will understand his condition, who may perhaps give him something to relieve present discomforts, but, more importantly, who may reassure him against his worst fears or, in any case, give him confidence that everything possible will be done to meet the situation. And is it not probable that the old-time family doctor, except in cases where a modern cure can be promised, filled this role about as well as is done today?

This basic human reaction of craving help in disease has existed since before the dawn of civilization and is obviously the reason for the existence of the medical profession.

In every community, however primitive, persons have appeared who by inherited teachings and by their own observation have become recognized as knowing more about disease than their fellows — medicine men or doctors — and although in past ages diagnosis, except in such obvious entities as measles, smallpox and tumors, was limited and there was little real treatment except palliation with opium, it seems probable that prognosis more nearly approached that of today. Thus when, in addition to opium as necessary, a patient could be given either reassurance or, in failing cases, advice about putting his affairs in order, was not this real professional service?

Even today, from the patient's viewpoint, when a man who is in a panic because he believes that he is about to die of pneumonia is given convincing assurance that he is mistaken, is that not comparable in value to a cure by penicillin? And when a patient dying of cancer comes to regard his doctor as something akin to a spiritual counselor, is that not professional service of an ageless sort?

Medical schools of today have more than they can do in their four years' course to teach medical science and its practical application in diagnosis and treatment, and so pay little attention to this more personal aspect of practice. Medical

meetings are devoted almost purely to advanced science. In fact, it would be difficult to teach the art of medicine in formal courses, yet it seems to me that more reference should be made to it, by example and otherwise, throughout the years of clinical instruction.

Friendliness and human sympathy are still the rule in medical practice, but should not this function of the medical profession be more strongly and repeatedly emphasized?

Boston, Massachusetts LOWIS W. PALFREY, M.D.

BOOK REVIEW

Plastic and Reconstructive Surgery: A Manual of Management. By Ferris Smith, M.D. 8°, cloth, 895 pp., with 591 illustrations. Philadelphia: W. B. Saunders Company, 1950. $15.00.

In the last three decades, plastic and reconstructive surgery, one of the latest specialties of surgery, has made great advances. This is undoubtedly due to two world wars, the tremendous increase in home, factory and transportation accidents and the increased public demand for corrective surgery of congenital deformities.

This text is written by a well known plastic surgeon of many years' experience and is a valuable addition to the growing collection of publications on this subject.

The preliminary chapters are devoted to a discussion of general topics such as the relative merits and indications of various types of grafts and pedicle flaps, and surgical technic. Chapters V to XIV present the operative treatment in various regions of the body from the scalp to the extremities. There are 592 illustrations, including line drawings and serial photographs from cases, which aid in understaning the text. One of the important features of the book is a detailed description of the various steps in operative procedures, and the author has, whenever possible, evaluated the various types of operations. He stresses the judicious use of local pedicle flaps in treatment of unsightly deformities of the face. He does not hesitate to stress the "don'ts" as well as the "do's" but is at times somewhat overzealous in this respect.

There is an extensive bibliography, arranged by topics to facilitate further reading on a subject; the index is very good.

This manual not only will be of value to the experienced plastic surgeon but also will be of assistance to the beginner with a good surgical background.

V. H. KAZANJIAN, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Dementia Praecox or The Group of Schizophrenias. By Eugen Bleuler, translated by Joseph Zinkin, M.D., with a foreword by Nolan D. C. Lewis, M.D. 8°, cloth, 548 pp. New York: International Universities Press, 1950. $7.50.

This is the first translation into English of Bleuler's important work, first published in Aschaffenburg's *Handbuch der Psychiatrie* in 1911 under the title of *Dementia Praecox oder die Gruppe der Schizophrenia.* A bibliography of 850 titles, contained in the original German edition, and a selected bibliography, 1911-1948, of twenty pages, compiled by the translator, are appended to the text. There is a good index and the book is well published. It should be in all collections on psychiatry.

Modern Abnormal Psychology: The Definitive and Dynamic Aspects of the Abnormal; The Neuroses and Psychoses. Edited by William H. Mikesell. 8°, cloth, 880 pp. New York: Philosophical Library, Inc., 1950. $10.00.

This semi-popular book is the joint work of twenty-five contributors. The history of mental diseases and the various neuroses, the principal psychoses, schizophrenia, manic-depression and evolutional melancholy are discussed. Diagnostic technic and various types of treatment are emphasized. Special attention is paid to frustrations, the principal types of defense mechanisms, the long or short forms of psychoanalysis, the technic practiced by the Non-Freudian group and the latest findings in psychosomatic medicine. All points of view of the Freudian, Non-Freudian and the Non-Analytical therapists are discussed impartially. Short lists of references are appended to the various chapters; there are indexes of authors and subjects, and the book is well published. It should be in all collections on the subject.

Humanism in an Age of Science, being a Ludwig Mond Lecture delivered at the Manchester School of Medicine on October 6, 1949. By John F. Fulton, O.B.E., M.D., LL.D., Sterling Professor of Physiology, Yale University. Publication No. 25. Historical Library, Yale University School of Medicine. 8°, paper, 26 pp. New York: Henry Schuman, 1950. $.75.

In this lecture Dr. Fulton makes an appeal for the publication of source materials in the field of science. The second part, on the inter-relation between science and literature, contains material of interest to the medical historian. The pamphlet should be in medical-history collections.

Clinical Applications of Suggestion and Hypnosis. By William T. Heron, M.A., Ph.D., professor of psychology, University of Minnesota, Minneapolis, Minnesota. 12°, cloth, 116 pp. Springfield, Illinois: Charles C Thomas, 1950. $3.00.

This monograph on the practical use of suggestion and hypnosis is intended for professional use only and not for general circulation. The greater part of the text is devoted to hypnosis. There is a bibliography of eleven pages, and an index. The small book should be in all collections on hypnotism.

Die Klinische Untersuchung Des Nervensystems. Von Prof. Dr. Med. G. H. Monrad-Krohn, F.R.C.P., direktor der Universitäts-Nervenklinik Oslo. Ausgabe in deutscher. Sprache herausgegeben und übersetzt von Dr. med. habil, Heinz Köbcke, dozent an der Universitat Tübingen. 8°, cloth, 383 pp., with 131 illustrations. Stuttgart: Georg Thieme Verlag, 1950. Preis: Ganzleinen DM 29.70.

This German translation of the ninth edition of the author's *Clinical Examination of the Nervous System,* an authoritative book, should prove valuable to German-reading neurologists. There are indexes of subjects and authors, and the book is well published.

Das Autogene Training (Konzentrative Selbstentspannung), Versuch Einer Klinisch-Praktischen Darstellung. Von Prof. J. H. Schultz, Nervenarzt, Berlin. 8°, cloth, 325 pp., with illustrations. Stuttgart: Georg Thieme Verlag, 1950. Ganzeinen DM 27.

The first edition of this work was published in 1932, and the previous edition in 1941. The text has been revised to bring it up to date. The references to the literature and case reports are incorporated throughout the text. There are indexes of authors and subjects. The book is well published and should be in all collections on psychiatry.

NOTICES

AMERICAN CONGRESS OF PHYSICAL MEDICINE

The American Congress of Physical Medicine will hold its twenty-ninth annual scientific and clinical session September 4, 5, 6, 7 and 8, 1951 inclusive, at the Shirley-Savoy Hotel, Denver, Colorado. Scientific and clinical sessions will be given on the days of September 4, 5, 6, 7 and 8, 1951. All sessions will be open to physicians and other professional personnel. In addition to the scientific sessions, the annual instruction seminars will be held September 4, 5, 6, and 7. These seminars will be offered in two groups. One set of ten lectures will consist of basic subjects and attendance will be limited to physicians. One set of ten lectures will be more general in character and will be open to physicians as well as to therapists, who are registered with the American Registry of Physical Therapists or the American Occupational Therapy Association. Full information may be obtained by writing to the American Congress of Physical Medicine, 30 North Michigan Avenue, Chicago 2, Illinois.

(*Notices concluded on page xiii*)